EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2024
EMA/355992/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Beyfortus

International non-proprietary name: Nirsevimab

Procedure No. EMEA/H/C/005304/II/0005

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	anti-drug antibody(ies)
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
Beyfortus	nirsevimab
CHD	congenital heart disease
CLD	chronic lung disease
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
HIV	human immunodeficiency virus
HR	hazard ratio
iCSR	interim clinical study report
ICU	intensive care unit
IDMC	independent data monitoring committee
IgG1κ	immunoglobulin gamma type 1, kappa
IM	intramuscular
IP	investigational product
LRTI	lower respiratory tract infection
MA	medically attended
MAA	Marketing Authorisation Application
mAb	monoclonal antibody
MEDI8897	nirsevimab
OR	odds ratio
NOCD	new onset chronic disease
PK	pharmacokinetic(s)
PT	preferred term
RSV	respiratory syncytial virus
SAE	serious adverse event
SmPC	Summary of Product Characteristics
TEAE	treatment-emergent AE
TESAE	treatment-emergent SAE
wGA	weeks gestational age
YTE	M252Y/S254T/T256E

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 4 April 2023 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of children up to 24 months of age who remain vulnerable to severe Respiratory Syncytial Virus (RSV) disease through their second RSV season for BEYFORTUS, based on interim results from studies D5290C00005 and D5290C00008.
Study D5290C00005 (MEDLEY) is a Phase II/III, randomized, double-blind, placebo-controlled study to evaluate the safety of Beyfortus in high-risk children. Study D5290C00008 (MUSIC) is a Phase II, open-label, uncontrolled, single-dose study to evaluate the safety and tolerability, pharmacokinetics, and occurrence of antidrug antibody for Beyfortus in immunocompromised children ≤ 24 Months of Age.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 2.1 of the RMP has also been submitted.
In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan market exclusivity

Similarity

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

Derogation(s) of market exclusivity

Not applicable.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Thalia Marie Estrup Blicher Co-Rapporteur: N/A

Submission date	4 April 2023
Start of procedure:	22 April 2023
CHMP Rapporteur Assessment Report	23 June 2023
PRAC Rapporteur Assessment Report	22 June 2023
PRAC members comments	28 June 2023
Updated PRAC Rapporteur Assessment Report	29 June 2023
PRAC Outcome	6 July 2023
CHMP members comments	10 July 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2023
Request for supplementary information (RSI)	20 July 2023
CHMP Rapporteur Assessment Report	13 September 2023
PRAC Rapporteur Assessment Report	13 September 2023
PRAC members comments	20 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur Assessment Report	5 October 2023
Request for supplementary information (RSI)	12 October 2023
Start of procedure:	27 November 2023
CHMP Rapporteur Assessment Report	20 December 2023
CHMP members comments	15 January 2024
Updated CHMP Rapporteur Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
Start of procedure:	26 February 2024
CHMP Rapporteur Assessment Report	21 March 2024
CHMP members comments	15 April 2024
Updated CHMP Rapporteur Assessment Report	18 April 2024
Request for supplementary information (RSI)	25 April 2024
Start of procedure:	1 May 2024
CHMP Rapporteur Assessment Report	15 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteur Assessment Report	27 May 2024

Request for supplementary information (RSI)	30 May 2024
Start of procedure:	05 June 2024
CHMP Rapporteur Assessment Report	12 June 2024
CHMP members comments	17 June 2024
Updated CHMP Rapporteur Assessment Report	17 June 2024
CHMP Opinion	27 June 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Respiratory syncytial virus is the most common cause of LRTI among infants and young children globally and is a major cause of hospital admission, with an estimated 33 million clinical cases and 3.6 million hospitalisations in children < 5 years of age globally in 2019 (Li et al 2022). This risk extends into the second RSV season, with an RSV-attributable hospitalisation rate for respiratory disease of approximately 2.5 per 1000 population estimated in children aged 6 to 23 months in the UK between 1995 and 2009 (Taylor et al 2016).

The only currently approved prophylaxis for RSV for children vulnerable to severe disease in their second season is palivizumab (SYNAGIS; EU approval 1999).

Beyfortus was approved in the EU on 31 October 2022 for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

This variation provides data for infants and children with CLD or CHD who received nirsevimab in their second RSV season.

State the claimed the therapeutic indication

The following wording is proposed for the SmPC:

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

1 Neonates and infants during their first RSV season.

2 Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include but is not limited to children with:

- *Chronic lung disease of prematurity*
- *Haemodynamically significant congenital heart disease*
- *Immunocompromised states*
- *Down syndrome*
- *Cystic fibrosis*
- *Neuromuscular disease*
- *Congenital airway anomalies.*

Beyfortus should be used in accordance with official recommendations.

2.1.2. About the product

Nirsevimab (MEDI8897) is a recombinant neutralising human IgG1κ long-acting mAb to the prefusion conformation of the 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 in antigenic site Ø on the prefusion protein with dissociation constants KD = 0.12 nM and KD = 1.22 nM for RSV subtype A and B strains, respectively. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

Current indication:

Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.

Beyfortus should be used in accordance with official recommendations.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The development programme is in compliance with the paediatric investigation plan.

2.1.4. General comments on compliance with GCP

The MAH claims that the study was carried out in accordance with the GCP guidelines. No issues were discovered during the assessment of the dossier that would request a GCP inspection.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1 *Summary of Nirsevimab Clinical Studies Referred to in the Summary of Clinical Pharmacology Studies Addendum*

Study number/ abbreviation Phase (Status)	Study design	Study population	Dosage regimen and route of admin	Sampling time points [a]	Number of subjects included in the analyses presented in this Addendum
D5290C00005 /MEDLEY Phase II/III Pivotal (Complete)	Randomised, double-blind, palivizumab-controlled, safety, descriptive efficacy, PK, and ADA	Infants and children entering their first or second RSV season, eligible to receive palivizumab. RSV Season 1: Preterm infants born < 35 wGA (without CLD or CHD) (referred as preterm cohort) and term and preterm infants with CLD or CHD (referred as CLD/CHD cohort). RSV Season 2: Children ≥ 12 and ≤ 24 months with CLD or CHD (in CLD/CHD cohort) who received nirsevimab or palivizumab in RSV Season 1 25 countries, including US and Japan	RSV Season 1 Refer to Table 2 in Module 2.7.2, MAA RSV Season 2 CHD/CLD cohort: Nirsevimab recipients in Season 1: nirsevimab 200 mg IM followed by 4 once-monthly placebo doses IM. Palivizumab recipients in Season 1, 1:1 re-randomised: nirsevimab 200 mg IM, followed by 4 once-monthly placebo doses IM or palivizumab 15 mg/kg IM (5 once-monthly doses)	PK Screening or Day 1 pre dose and Days 8 (Japan only), 15 (EU only) and/or 31 (non-EU), Days 151, and 361. ADA Screening or Day 1 pre dose, Day 31, 151, and 361. Resistance analyses Within approximately 2 days after healthcare provider assessment and diagnosis or hospitalisation [b]	Included in PK/ADA analyses: Season 1 Refer to Table 2 in Module 2.7.2, MAA Season 2 (CLD/CHD cohort): Nirsevimab/nirsevimab: 180/180 Palivizumab/nirsevimab: 40/40 Included in resistance analysis population: [c] Season 1 Nirsevimab: 12 Palivizumab: 10 Season 2 (CLD/CHD cohort) Nirsevimab/Nirsevimab: 180 Palivizumab/Palivizumab: 42 Palivizumab/Nirsevimab: 40
D5290C00008 /MUSIC Phase II (Complete)	Open-label, uncontrolled, single-dose study, safety, descriptive efficacy, PK, and ADA	Immunocompromised neonates, infants and children ≤ 24 months of age: In their first year of life AND entering their first RSV season at the time of dose administration OR In their second year of life AND entering their second RSV season at the time of dose administration 6 countries, including US and Japan	1st year of life cohort: Nirsevimab: 50 mg or 100 mg single IM dose [d] 2nd year of life cohort: Nirsevimab: 200 mg IM single dose (2 x 100 mg)	PK, ADA Screening or Day 1 pre dose, Day 8 (PK only, in Japan only), Day 31, 151, and 361 Resistance analyses Within approximately 2 days after healthcare provider assessment and diagnosis or hospitalisation [b]	Included in final PK/ADA: A total of 100 non-randomised, immunocompromised subjects received the proposed dose of nirsevimab 1st year of life cohort: Nirsevimab 50 mg/100 mg: 46 2nd year of life cohort: Nirsevimab 200 mg: 54[e] Included in resistance analysis population: [c] 1st year of life cohort: Nirsevimab 50 mg/100 mg: 2 2nd year of life cohort: Nirsevimab 200 mg: 1

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

[b] Nasal samples were to be collected within approximately 2 days after the initial healthcare provider assessment and diagnosis of LRTIs (inpatient or outpatient) and from all subjects hospitalised with any respiratory infection (upper or lower).

[c] The resistance analysis population included all randomised and dosed subjects with a central lab RT-PCR-positive RSV and an evaluable NGS sequence.

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

[e] The total of 54 subjects in the second year of life in MUSIC includes 2 subjects enrolled in the second year of life group (both aged 12.3 months), who mistakenly received 50% of the full, planned dose (100 mg instead of 200 mg).

ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; EU = European Union; IM = intramuscular; LRTI = lower respiratory tract infection; MAA = Marketing Authorisation Application; NGS = next generation sequencing; PK = pharmacokinetics; RSV = respiratory syncytial virus; RT-PCR = reverse transcription polymerase chain reaction; US = United States; wGA = weeks gestational age.

Beyfortus was approved in the EU on 31 October 2022 for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. Approval was based primarily on data from the Phase IIb Study D5290C00003 (Study 3) in very and moderately preterm infants born ⩾ 29 to < 35 wGA and the Phase III Study D5290C00004 (MELODY) in term and late preterm infants born ⩾ 35 wGA (Primary Cohort). In addition, RSV Season 1 data were available from Study D5290C00005 (MEDLEY) for infants with haemodynamically significant CHD, CLD of prematurity, and prematurity (< 35 wGA at birth), including extreme prematurity (< 29 wGA at birth).

A Type II variation was submitted on 11 November 2022 (procedure number EMEA/H/C/005304/II/0001) to update efficacy and safety results for MELODY (All Subjects) with new data for an additional 1522 subjects, unavailable at the time of the original MAA. The original MAA and this first variation support the benefit-risk of nirsevimab in infants through their first RSV season.

This variation concerns an extension of the indication for prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. There are data provided for infants and children with CLD or CHD who received nirsevimab in their second RSV season in MEDLEY, which includes children who received a second dose of nirsevimab (ie, subjects who were dosed with nirsevimab in both RSV Season 1 and RSV Season 2). Data are also presented from the Phase II open-label MUSIC study for immunocompromised infants and children up to 24 months of age who received nirsevimab in their first or second RSV season.

MEDLEY evaluated the safety and PK of nirsevimab in a higher-risk (palivizumab-eligible) population. No formal hypothesis testing for efficacy was intended in MEDLEY. The efficacy of nirsevimab in this population was assessed by PK extrapolation, as agreed per Committee for Human Products for Medicinal Use advice. Efficacy was extrapolated to infants in their first RSV season, including infants with CHD and CLD, in the MAA. MUSIC evaluated safety and PK in immunocompromised children entering their first or second RSV season. A similar PK extrapolation approach was taken for MUSIC. The pediatric studies used sparse PK-sampling.

2.3.2. Pharmacokinetics

Analytical methods

The previously validated bioanalytical and immunogenicity methods, described in the MAA of nirsevimab, were also applied in the clinical studies reported in this variation II application, see Table 2.

Table 2. MELODY (Study D5290C00004), MEDLEY (Study D5290C00005), and MUSIC (Study D5290C00008) PK and Immunogenicity Final Bioanalysis Reports

Study	Analyte	Matrix	Method	Study Bioanalytical Report
MELODY (Study D5290C00004)	Nirsevimab	Serum	ICD 817	RNIJ
MELODY (Study D5290C00004)	ADA against nirsevimab	Serum	ICDIM 419	RNIK
MELODY (Study D5290C00004)	ADA against YTE	Serum	ICDIM 421	RNIM

MELODY (Study D5290C00004)	nAb against nirsevimab	Serum	ICDIM 420	RNIL
MEDLEY (Study D5290C00005)	Nirsevimab	Serum	ICD 817	RNIN
MEDLEY (Study D5290C00005)	ADA against nirsevimab	Serum	ICDIM 419	RNIO
MEDLEY (Study D5290C00005)	ADA against YTE	Serum	ICDIM 421	RNIQ
MEDLEY (Study D5290C00005)	nAb against nirsevimab	Serum	ICDIM 420	RNIP
MEDLEY (Study D5290C00005)	Palivizumab	Serum	ICD 173	ROEE
MEDLEY (Study D5290C00005)	ADA against Palivizumab	Serum	ICDIM 65	ROEF
MUSIC (Study D5290C00008)	Nirsevimab	Serum	ICD 817	RQUJ
MUSIC (Study D5290C00008)	ADA against nirsevimab	Serum	ICDIM 419	RQUK
MUSIC (Study D5290C00008)	ADA against YTE	Serum	ICDIM 421	RQUM
MUSIC (Study D5290C00008)	nAb against nirsevimab	Serum	ICDIM 420	RQUL

ADA = anti-drug antibody; nAb = neutralizing antibody.

Immunogenicity in all clinical studies of nirsevimab was assessed in a tiered manner: first in the ADA assay, an electrochemiluminescent (ECL) immunoassay, followed by secondary testing for neutralizing antibodies (nAB) against nirsevimab and ADAs directed against the YTE modification, see

Table 3 with the number of study samples analysed in the different immunogenicity assays and the number of the samples identified as positives.

Table 3 **MELODY (Study D5290C00004), MEDLEY (Study D5290C00005), and MUSIC (Study D5290C00008); Bioanalytical Samples Tested and Number of Positive Samples**

Study	Analyte	Number of Reported Positive Samples	Number of Samples Analysed [a]	Study Bioanalytical Report
MELODY (Study D5290C00004)	ADA against nirsevimab	157	10727	RNIK
	ADA against YTE	116	132 [a]	RNIM
	nAb against nirsevimab	34	157	RNIL
MEDLEY (Study D5290C00005)	ADA against nirsevimab	52	2526	RNIO
	ADA against YTE	42	47 [a]	RNIQ
	nAb against nirsevimab	3	46 [a]	RNIP
MUSIC (Study D5290C00008)	ADA against nirsevimab	11	372	RQUK
	ADA against YTE	11	11	RQUM
	nAb against nirsevimab	1	6 [a]	RQUL

[a] Due to samples exceeding freeze thaw stability or being depleted in previous PK and ADA analysis it was not possible to analyze all ADA positive samples in the anti-YTE and nAb ADA characterization assays. Further details are documented in the bioanalytical reports referenced in the table.

ADA = anti-drug antibody; nAb = neutralizing antibody.

Modelling and simulation analyses

Nonlinear mixed-effects modeling software NONMEM® (version 7.4.3, ICON, Hanover, MD, US), was used for popPK modelling. The first-order conditional estimation method of NONMEM with interaction (FOCE INTER) was used for PK model development during analysis. Perl-Speaks-NONMEM (PsN; Department of Pharmacy, Uppsala University, Uppsala, Sweden, version 4.8.1) was used for facilitation of NONMEM tasks, such as covariate testing.

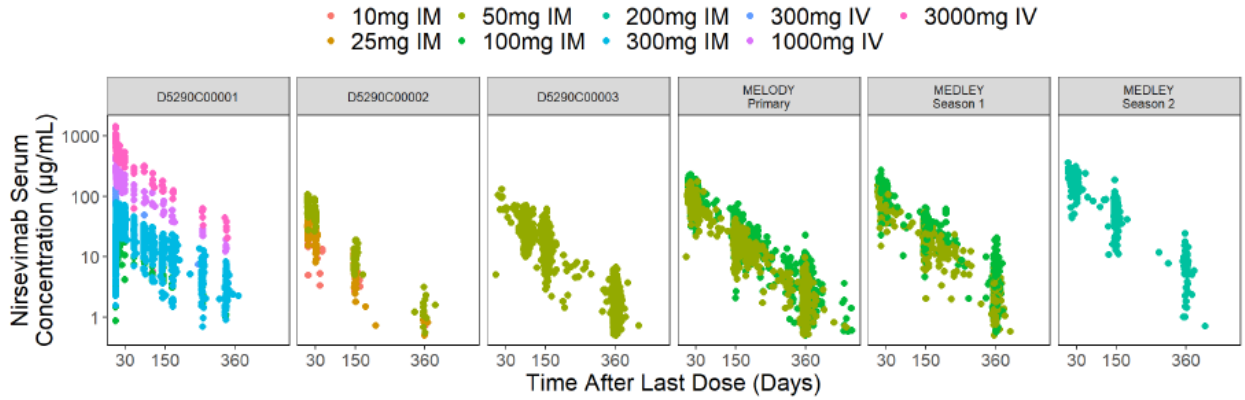
R (R Core Team [2020] was used for simulations, graphical analysis, model diagnostics, and statistical summaries. All simulations were carried out in R with the RxODE package.

MELODY and MEDLEY

A previous population pharmacokinetic model for nirsevimab was built on serum pharmacokinetic data from healthy adults and preterm infants in Phases 1, 1b/2a, 2b, and 3 studies (Studies D5290C00001, D5290C00002, D5290C00003, D5290C00004 [MELODY], and D5290C00005 [MEDLEY]). This present analysis updated the previous models to include additional data from the MELODY study and all MEDLEY Season 1 and Season 2 data (Final DBL) from CHD/CLD patients.

The PK analysis dataset included 9597 measurable PK observations from 3133 subjects. A total of 1030 PK observations and 499 subjects were excluded. Of these were 37.7% post-dose BLQ. All PK data from the Safety cohort of MELODY was excluded (481 samples from 444 subjects). Data from 55 subjects who underwent cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 were also excluded along with data from 18 MEDLEY subjects from Season 2 with apparent dosing or sample issues. Fifteen measurements from MELODY and 1 PK measurement from MEDLEY were excluded from the dataset due to use of expired PK kits. The updated popPK analysis was conducted on a database containing 2683 subjects with 8987 PK observation records.

Figure 1 Nirsevimab Serum Concentration Versus Time by Study



Source: ASTR-CP-2207-MEDI8897-bla-EDA-plots-music-22Jul2022.Rmd
Notes: Subjects who received palivizumab in Season 1, received 200 mg as their first nirsevimab dose.
Abbreviations: IM=intramuscular; IV=intravenous

Nirsevimab serum concentration data were previously described by a 2-compartment PK model with first-order elimination. IM absorption was described by a first-order process, and IM bioavailability was estimated (IV data only available in adults). In addition to allometrically scaling clearances (CLs) and volumes with body weight, the effect of postmenstrual age (maturation) on CL was modelled using an asymptotic exponential function centred at the postmenstrual age of a full-term infant. The previous popPK model including all previous exclusions was re-estimated with additional MELODY Primary cohort data, Day 361 MEDLEY Season 1 data, and Season 2 MEDLEY study data.

Race effects included on both CL and central volume of distribution (V2) were simplified by grouping races with similar effects. Effect of ADA (categorical) was included on CL. Inter-individual variability (IIV) was included on CL, V2 and absorption rate constant (Ka). An additive error on log-scale (approximately proportional) was used. Random variability to describe IIV, ETA, shrinkage was low to moderate for CL (11%) and V2 (27%) but high for Ka (83%), most likely due to the lack of data informing Ka in the paediatric subjects. Allometric exponents for clearances and volumes were estimated to 0.644 and 0.853. A trend of underprediction of Season 2 data resulted in a “Season 2” covariate was added on CL. Parameters of the final updated model is shown in Table 4.

Table 4 Final Model Parameter Estimates

Parameters	Estimates	%RSE	Bootstrap 95% CI
Clearance (CL, mL/day) [a]	38.8	6	29.9, 43.9
Central volume of distribution (V2, mL) [a]	1980	10	567, 2760
Intercompartmental clearance (Q, mL/day) [a]	709	9	462, 872
Peripheral volume of distribution (V3, mL) [a]	2400	5	1980, 2790
Absorption rate constant (KA, day^{-1}) [b]	0.401	7	0.206, 0.504
Bioavailability (F)	0.839	7	0.627, 0.939

Covariate	Estimates	%RSE	Bootstrap 95% CI
Fractional clearance (BETACL)[c]	0.364	6	0.312,3 0.416
Maturation half-life (TCL, months)[c]	14.8	9	10.9, 20.0
Body weight effect on clearances (CL, Q)[d]	0.589	3	0.526, 0.646
Body weight effect on volumes (V2, V3)[d]	0.84	1	0.806, 0.863
Race effect on clearance (Black or African American, Other)[e]	CL_{pop}* (1 + 0.132)	8	0.111, 0.153
Race effect on clearance (Asian, Ame.Ind. or Ala.Nat., Multiple races) [e]	CL_{pop}* (1 - 0.0894)	30	-0.123, -0.0545
Race effect on volume of distribution (Asian, Ame.Ind. or Ala.Nat., Multiple races) [e]	$V2_{pop}$* (1 - 0.226)	24	-0.580, -0.141
Season 2 effect on clearance	CL_{pop}* (1 - 0.122)	7	-0.159, -0.0825
Categorical ADA effect (yes or no per subject) on CL	CL_{pop}* (1 + 0.124)	12	0.0890, 0.158
Random Effects	**Estimates (%CV)**	**%RSE [%Shrinkage]**	**Bootstrap 95% CI**
IIV on CL	26	2 [10%]	24, 27
ηV2-ηCL correlation	r = 0.785	-	
IIV on V2	43	4 [29%]	32, 90
IIV on KA	44	8 [83%]	16, 78
Residual Error	**Estimates**	**%RSE**	
Proportional error	21%	1	20, 22

Source: run443.lst, sumo-run443.txt

[a] Parameter estimates for a 70 kg adult. The derived parameters for an infant of 5 kg, 11.1 months postmenstrual age are CL = 3.42 mL/day, V2 = 216 mL, Q = 150 mL/day, and V3 = 261 mL.

[b] Absorption $t_{½}$ (ln(2)/KA) = 1.7 days.

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

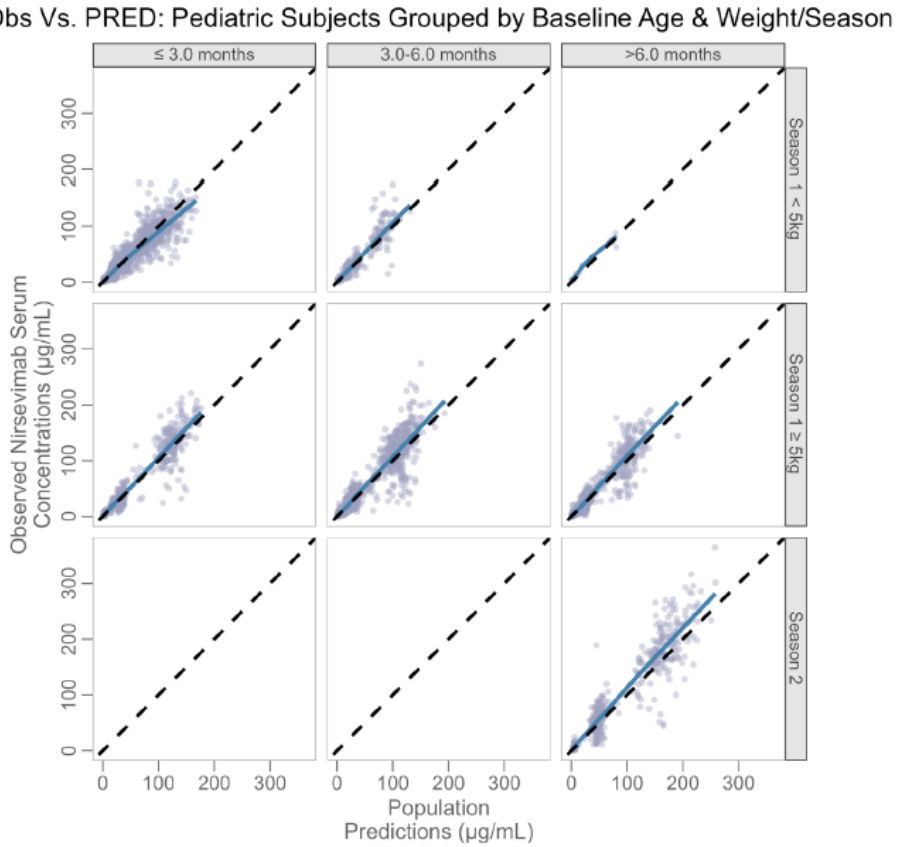
[d] Weight effect function: $(WT/70)^{parameter\ estimate}$

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

Abbreviations: η=eta; %CV=percent coefficient of variation; %RSE=percent relative standard error; ADA=antidrug antibody; CI=confidence interval; CL_{pop}=typical CL; IIV=inter-individual variability; r=correlation coefficient; $t_{½}$=half-life; $V2_{pop}$=typical V2; V2=Vc = central volume; V3=Vp = peripheral volume, WT=body weight

The final re-estimated model was evaluated by GoF plots, nonparametric bootstrap analysis (1000 replicates) and by VPCs.

Figure 2 Observed Versus Population Predicted Stratified by Weight, Season, and Agen Group at Time of Dosing

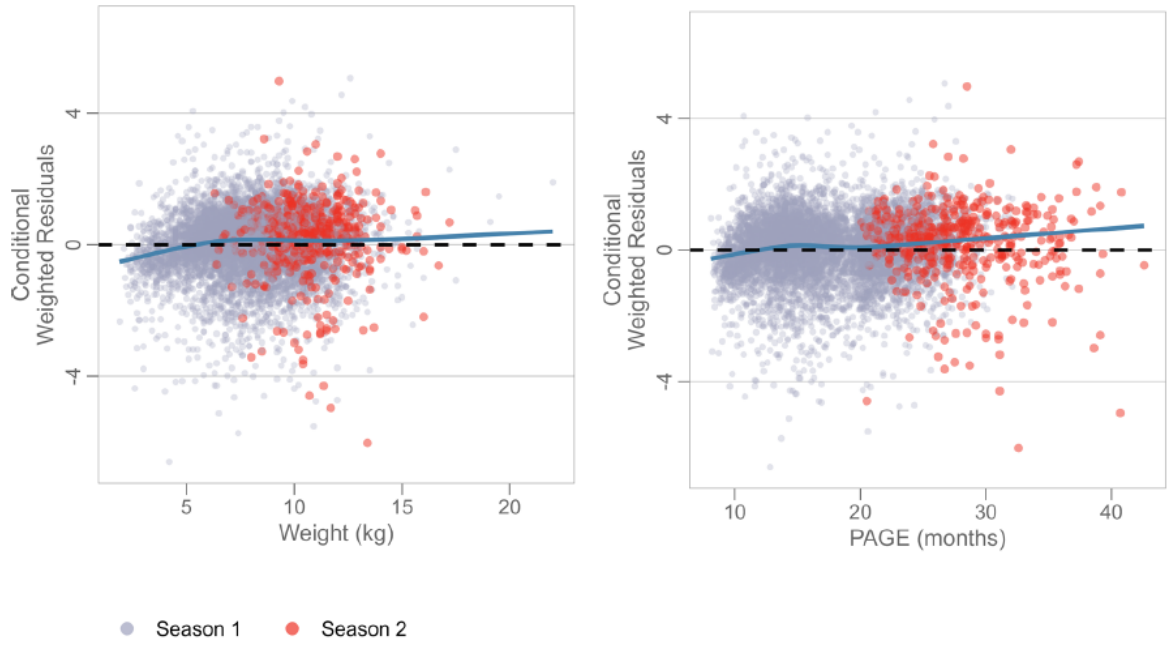


Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443)

Notes: Dots are individual data points for pediatric subjects, solid blue lines are smoothed LOESS lines. The dashed lines are lines of identity.

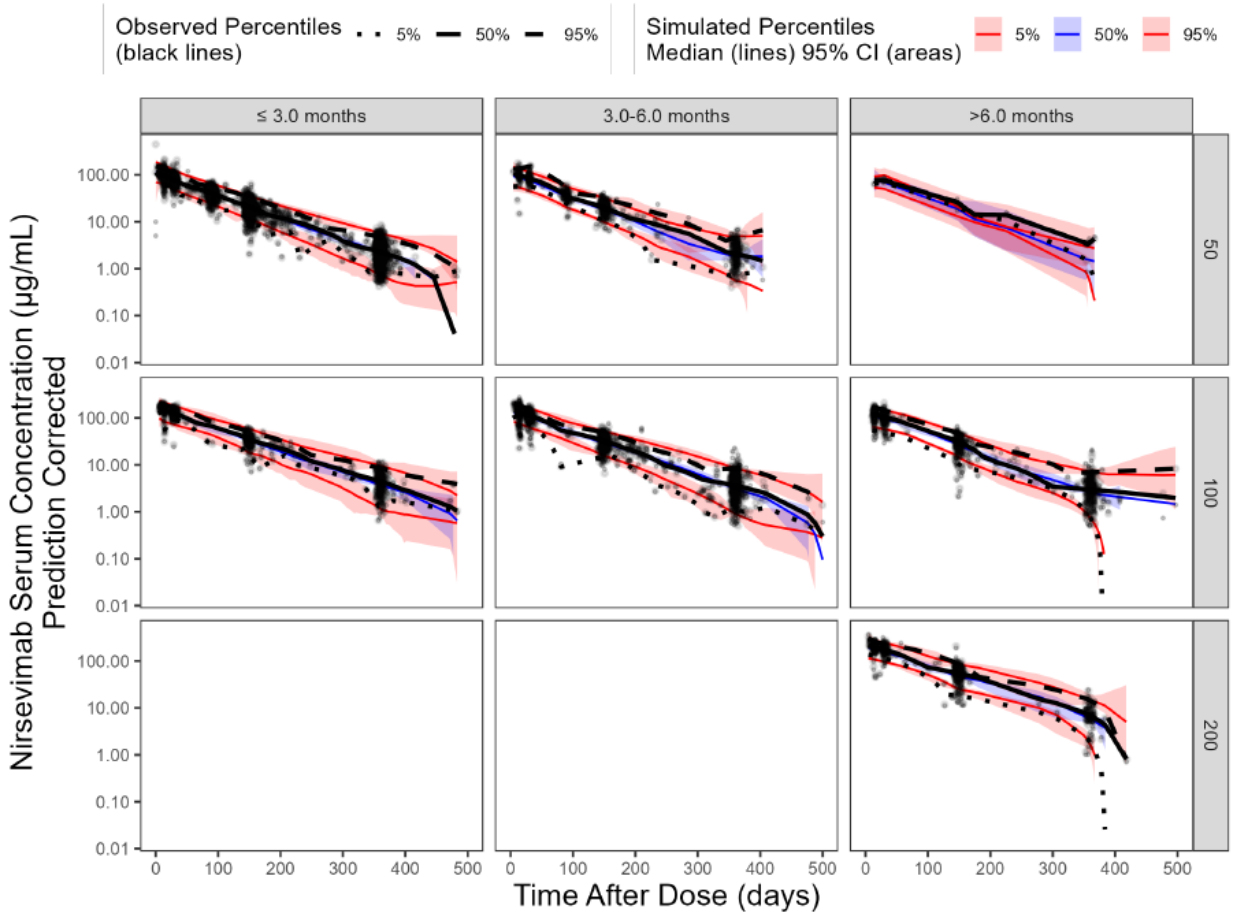
Abbreviations: LOESS=locally weighted smoothing; Obs=observed; PRED=population prediction

Figure 3 GOF Plots of Conditional Weighted Residuals vs Weight and PAGE for Pediatric Subjects in the Final Model by Season



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443)
Notes: Dots are individual data points for pediatric subjects. Solid blue lines are smoothed LOESS lines. Horizontal lines are reference lines.
Abbreviations: CWRES=conditional weighted residuals; GOF=goodness-of-fit; LOESS=locally weighted smoothing; PAGE=post-menstrual age

Figure 4 Prediction-Corrected VPC for the Final Model Stratified by Agen and Dose



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443)

Notes: Black dots are observed data points for pediatric subjects with weight <5kg receiving 50mg, weight ≥5kg receiving 100mg in Season 1, or subjects receiving 200mg in Season 2. Black solid line is the observed median. Black dotted and dashed lines are observed 5th and 95th percentiles, respectively. The blue shaded area is the 95% PI of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).

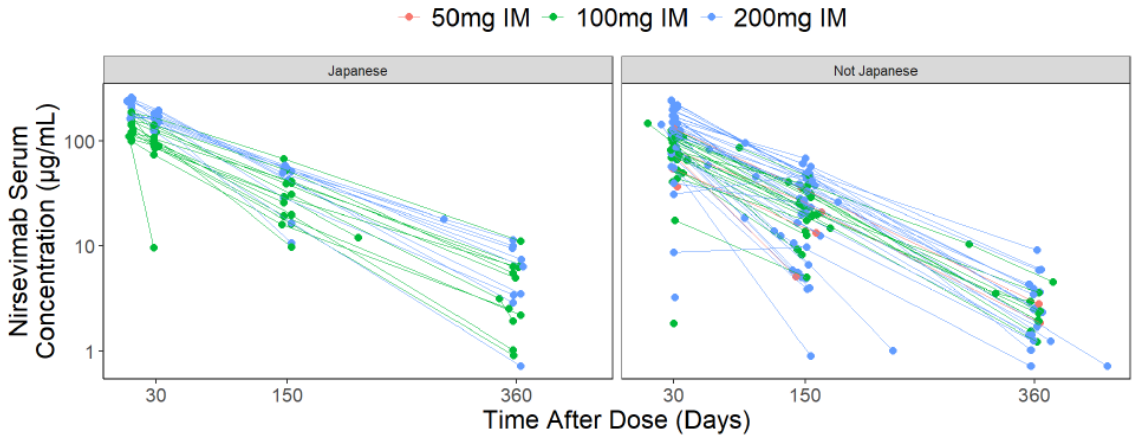
Abbreviations: CI=confidence interval; PI=prediction interval; VPC=visual predictive check

Previous models build on data from MEDLEY and MELODY were updated to describe nirsevimab population PK. The model structure was a 2-compartment model with linear elimination and IM absorption. CL and V were allometric scaled with body weight while effect of postmenstrual age was described by a maturation CL function. Other covariates included were effects of ADA status and race. Effect of race on Cl and V were grouped to simplify the model. Additional data collected in MELODY and MEDLEY (incl. Season 2 data) were included in the data set and all model parameters were re-estimated. The initial model underpredicted the Season 2 data from MEDLEY and a “covariate effect” of Season 2 on CL was included to compensate for this. The final updated model was evaluated by bootstrap. The GoF plots and VPCs for the final model indicated the final model could adequately describe nirsevimab PK in MEDLEY and MELODY.

MUSIC

In MUSIC, PK data were available from immunocompromised (IC) children aged 0 to 24 months collected in 97 subjects dosed in their first RSV season (6 with 50mg and 40 with 100mg) and 50 dosed in their 2nd RSV season (200 mg). Figure 5 Nirsevimab Serum Concentration in MUSIC Versus Time by Japanese Status show the individual serum concentrations by Japanese status.

Figure 5 Nirsevimab Serum Concentration in MUSIC Versus Time by Japanese Status

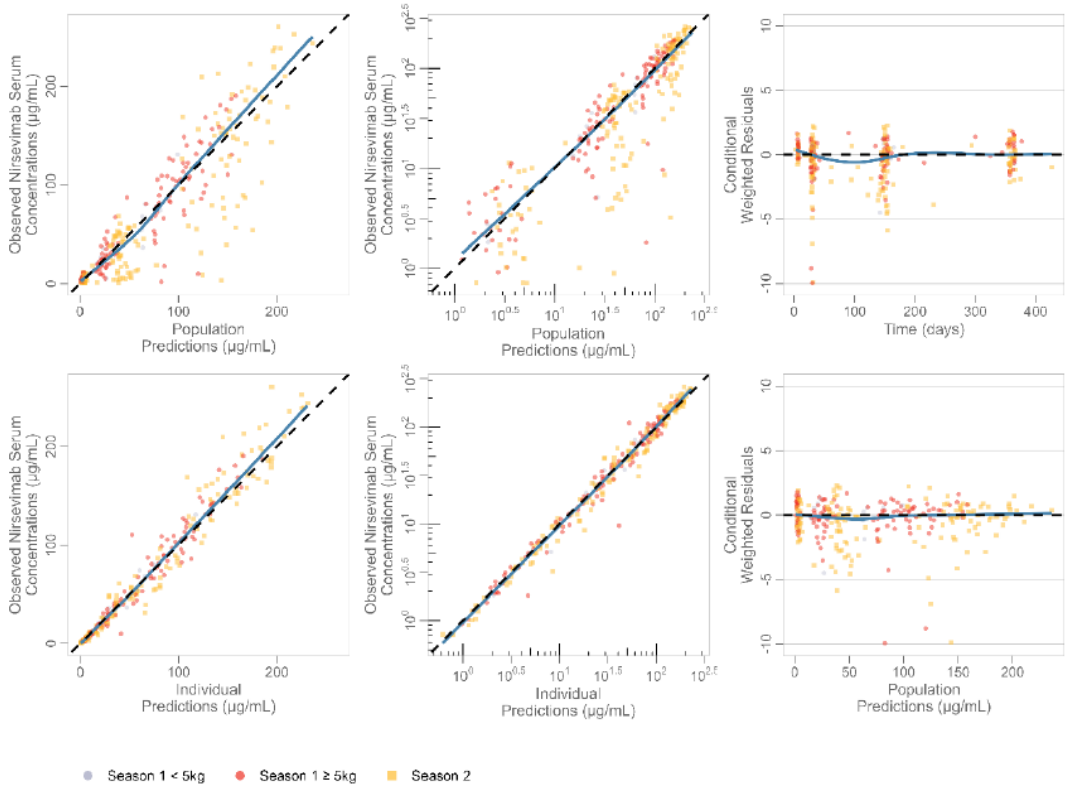


Source: ASTR-CP-2207-MEDI8897-EDA-RegQuestions-May2023.Rmd, ASTR-CP-2207-MEDI8897-EDA-RegQuestions-May2023.html
Abbreviations: IM=intramuscular

A total of 273 measurable PK observations were available at the data cut-off (16 May 2022). One subject from Season 1 was excluded from analysis, as all PK measurements were BLQ.

The final popPK model was used to perform a Bayesian Posthoc prediction of the PK data in MUSIC. GoF plots for the prediction are shown in Figure 6 GOF Plots for in Immunocompromised Children (MUSIC) for Predicted Observations (MAXEVAL=0) by Weight and Season.

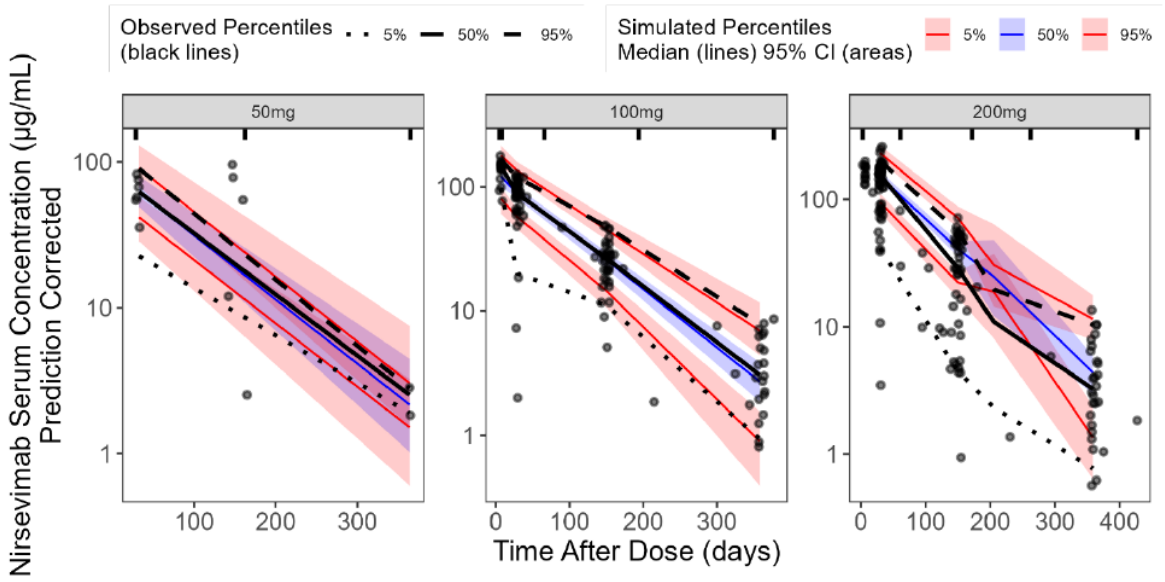
Figure 6 GOF Plots for in Immunocompromised Children (MUSIC) for Predicted Observations (MAXEVAL=0) by Weight and Season



Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)
Notes: Dots are individual data points for MUSIC subjects (red= Season 1 ≥5 kg, gray= Season 1 <5 kg, yellow: Season 2), and solid blue lines are smoothed LOESS lines. The dashed lines in columns 1 and 2 are lines of identity. In the 2 plots on the right, horizontal lines are reference lines.
Abbreviations: GOF=goodness-of-fit; IC=immunocompromised; LOESS=locally weighted smoothing

The final popPK model was used to generate 1000 replicate simulated profiles from the popPK modeling dataset (using MAXEVAL=0). Visual predictive check plots were presented by dose in Figure 7.

Figure 7 Prediction-corrected VPC; Prediction of MUSIC study based on Final PopPK model by Dose



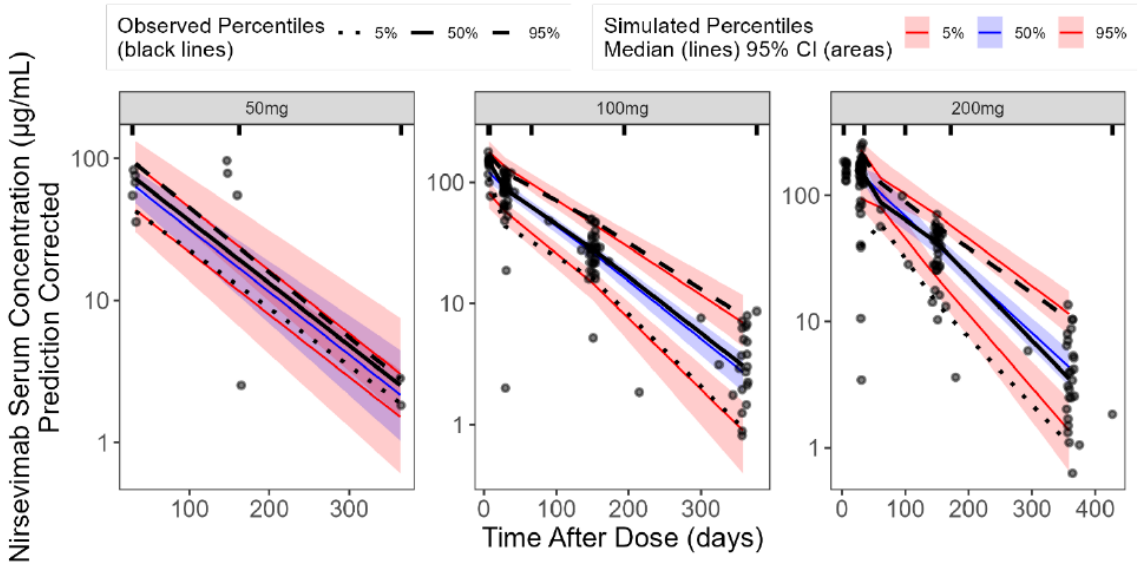
Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)

Notes: Black dots are observed data points for pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg. Black solid line is the observed median. Black dotted and dashed lines are observed 5th and 95th percentiles. The blue shaded area is the 95% PI of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).

Abbreviations: CI=confidence interval; IC=immunocompromised; PI=prediction interval; VPC=visual predictive check

14 subjects were identified as outliers, with an indication of a more rapid decline in serum concentration over time, based on visual inspection of the data.

Figure 8 Prediction-corrected VPC; Prediction of MUSIC study based on Final PopPK model by Dose (outliers excluded)



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

Notes: Black dots are observed data points for pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg. Black solid line is the observed median. Black dotted and dashed lines are observed 5th and 95th percentiles. The blue shaded area is the 95% PI of the simulated median (blue line), and pink shaded areas are the 95% PI of the simulated 5th and 95th percentiles (red lines).

Abbreviations: CI=confidence interval; IC=immunocompromised; PI=prediction interval; VPC=visual predictive check

To investigate the impact of clinical conditions which are potentially associated with protein loss and increased clearance of nirsevimab, the population PK model was subsequently updated with final data from the MUSIC study and parameters re-estimated (Table 5).

Table 5 Summary of Final Population PK Model Parameter Estimates, Model Updated with Study D5290C00008 – MUSIC Data

	Previous model		Updated model	
Parameters	**Estimates**	**%RSE**	**Estimates**	**%RSE**
Clearance (CL, mL/day) [a]	38.8	6	39	2.4
Central volume (Vc, mL) [a]	1980	10	2510	5.22
Intercompartmental clearance (Q, mL/day) [a]	709	9	541	9.48
Peripheral volume (Vp, mL) [a]	2400	5	2020	5.35
Absorption rate constant (KA, day-1) [b]	0.401	7	0.639	14.2
Bioavailability (F)[c]	0.839	7	0.839	-

Table 5 Summary of Final Population PK Model Parameter Estimates, Model Updated with Study D5290C00008 – MUSIC Data

	Previous model		Updated model	
Parameters	**Estimates**	**%RSE**	**Estimates**	**%RSE**
Covariate	**Estimates**	**%RSE**		
Fractional clearance (BETACL) [d]	0.364	6	0.364	5.89
Maturation half-life (TCL, months) [d]	14.8	9	15.2	8.41
Body weight effect on clearances (CL, Q) [e]	0.589	3	0.588	3.32
Body weight effect on volumes (Vc, Vp) [e]	0.84	1	0.862	0.891
Race effect on clearance (Black or African American, Other) [f]	CL_{pop}* (1 + 0.132)	8	CL_{pop}* (1 + 0.136)	7.77
Race effect on clearance (Asian, American Indian or Alaskan Native, Multiple races) [f]	CL_{pop}* (1 - 0.0894)	30	CL_{pop}* (1 - 0.0852)	25.9
Race effect on volume of distribution (Asian, American Indian or Alaskan Native, Multiple races) [f]	Vc_{pop}* (1 - 0.226)	24	Vc_{pop}* (1 - 0.166)	22.6
Season 2 effect on clearance	CL_{pop}* (1 - 0.122)	7	CL_{pop}* (1 - 0.0992)	8.36
Categorical ADA effect (yes or no per subject) on CL	CL_{pop}* (1 + 0.124)	12	CL_{pop}* (1 + 0.129)	11.2
Random Effects	**Estimates (%CV)**	**%RSE [%Shrinkage]**	**Estimates (%CV)**	**%RSE [%Shrinkage]**
IIV on CL	26	2 [10%]	27.1	1.39[9.6%]
ηVc-ηCL correlation	r = 0.785	-	r = 0.715	
IIV on Vc	43	4 [29%]	35	4.19[29.9%]
IIV on KA	44	8 [83%]	177	3.45[67.7%]
Residual Error	**Estimates**	**%RSE**		
Proportional error	21%	1	20.8	0.586

[a] Parameter estimates for a 70 kg adult. The derived parameters for an infant of 5 kg, 11.1 months postmenstrual age are CL = 3.42 mL/day, Vc= 216 mL, Q = 150 mL/day, and Vp= 261 mL.

[b] Absorption $t_{1/2}$ (ln(2)/KA) = 1.7 days.

[c] Bioavailability for the updated model has been FIXed to achieve comparability between models.

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

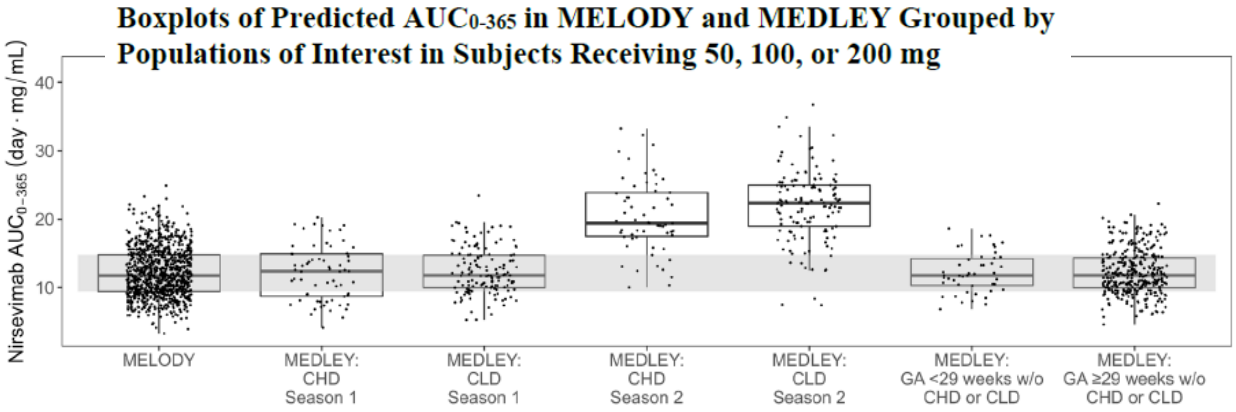
[e] Weight effect function: $(WT/70)^{\text{parameter estimate}}$.

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

Exposure simulations

In MEDLEY Season 2 (only including subjects with CHD or CLD), CL appeared to be lower than expected based on body weight and post-menstrual age, as evidenced in the underprediction of Season 2 Day 151 and Day 360 data which is why a "Season 2" covariate was included in the Pop PK model. The PK data in Season 2 was also more variable than in Season 1. Figure 9 and shows exposures based on post-hoc predicted parameters for subjects in MELODY, MEDLEY and MUSIC.

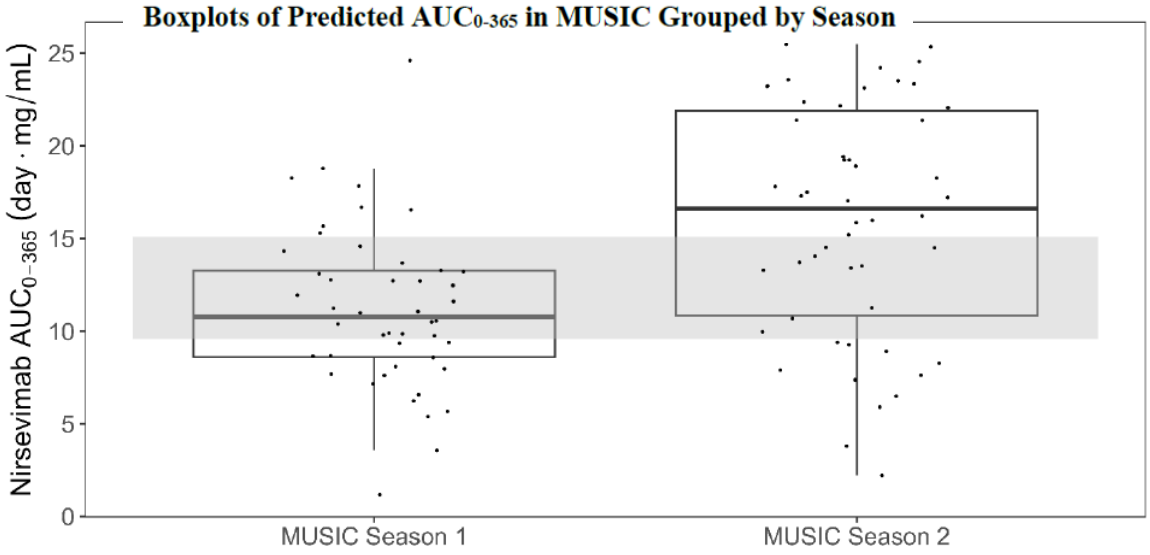
Figure 9



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R

Notes: Grey band is the reference inter-quartile range for MELODY AUC_{0-365}. Data presented are pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's syndrome) and was excluded for extrapolation. The 2 groups on the right, MEDLEY: GA <29 weeks w/o CHD or CLD and MEDLEY: GA ≥29 weeks w/o CHD or CLD, contain only Season 1 subjects.

Abbreviations: AUC_{0-365}=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; CHD=congenital heart disease; CLD=chronic lung disease; GA=gestational age; w/o=without



Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)
Notes: Grey band is the reference inter-quartile range for MELODY AUC_{0-365}. Subjects 4305001 and 7005002 (MUSIC) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; AUC_{0-365} were 18.3 and 12.5, respectively. Data presented are pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg.
Abbreviations: AUC_{0-365}=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model

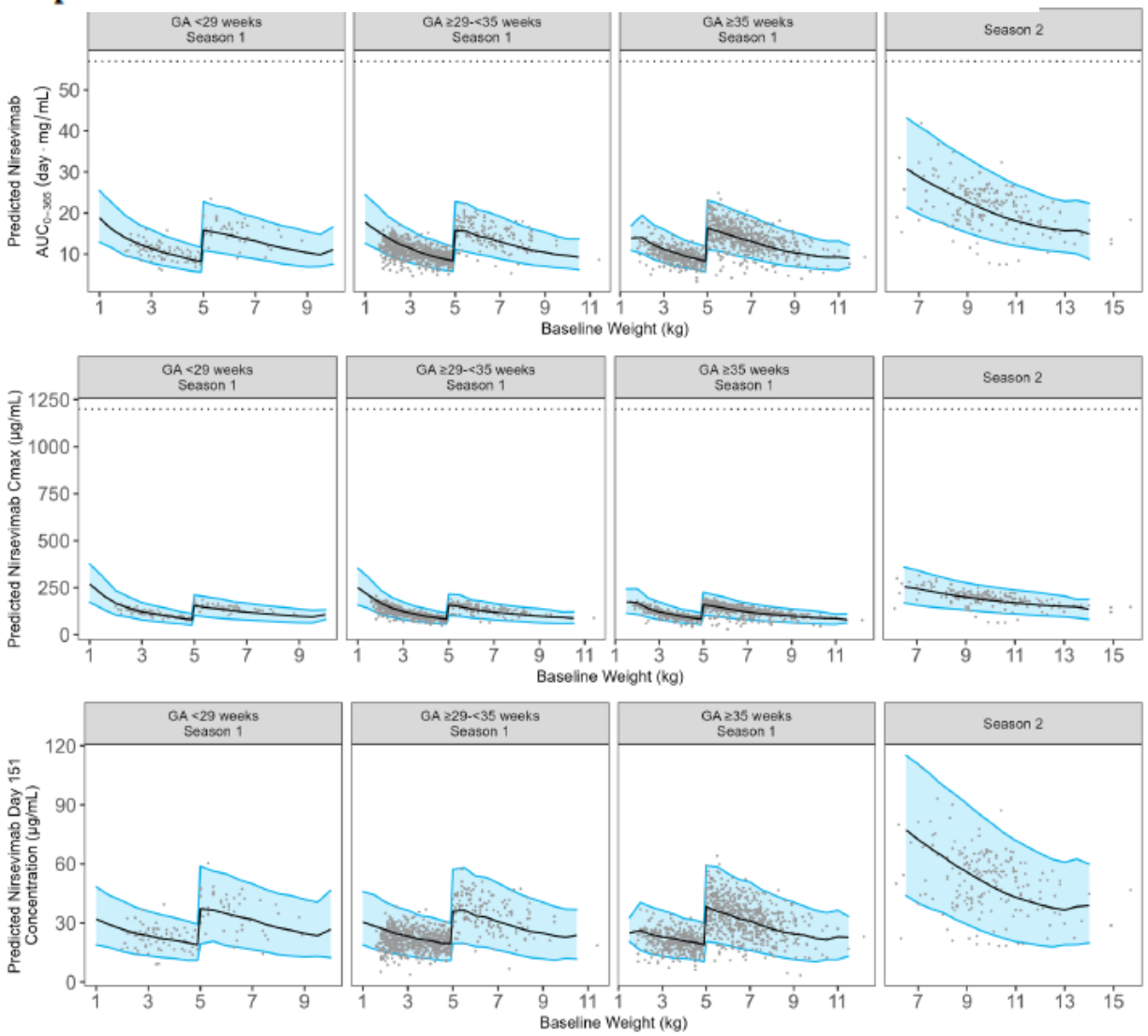
Simulations were performed based on the final popPK model to evaluate the nirsevimab dosing (Season 1: 50 mg for those weighing <5 kg and 100 mg for infants weighing ≥5kg, and Season 2: 200 mg) across age and weight ranges. AUCbaselineCL, AUC0-365, Cmax and concentration on Day 151 (end of RSV season) were derived for exposure metrics. Simulations were performed by creating virtual subjects with individual parameters derived from the typical values, relevant covariates, and between-subject variability from the final popPK model. Residual variability and parameter uncertainty were not included.

Subjects for each virtual population were generated from a uniform distribution across all ages within the group using the childsds R package. Infants (≥1 kg) were dosed according to baseline weight at time of dosing: Season 1: 50 mg for subjects <5 kg and 100 mg for infants ≥5 kg, and Season 2: 200 mg. For these simulations, it was assumed that infants being dosed in the second season had not received a previous dose in the first season.

Similar E-R relationship between nirsevimab serum concentration and RSV neutralizing ability is expected across all age groups. In addition, similar safety is expected across age groups because nirsevimab does not bind to any internal targets. The Applicant stated that if the proposed dose (200mg for infants entering their second RSV season) in the target palivizumab-eligible population resulted in serum nirsevimab concentrations at or above the predicted efficacious level demonstrated to be effective in preterm and term infants the extrapolation of these safety and efficacy data were considered demonstrated.

Figure 11

Predicted Exposure Versus Weight at the Time of Dose by Gestational Age Group and Season With 90% Prediction Intervals



Source: medi8897-sims-bla-08Aug2022.R

Notes: Blue bands are covering the 5th to 95the percentiles of the predictions for weight band dosing in Season 1, 200 mg in Season 2. Solid black lines are the predicted medians. Grey dots are individual predictions based on posthoc parameters from the final model for subjects in Study D5290C00003 <5kg, MELODY and MEDLEY. Dotted black lines are the median posthoc predicted exposure achieved in adults following 3000 mg IV dose (AUC_{0-365}: 57.0 day•mg/mL; Cmax: 1140 µg/mL). Season 2 simulations assume no prior dosing in Season 1.

Abbreviations: AUC_{0-365}=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; C_{max}=maximum serum concentration; GA=gestational age

From the boxplots of predicted AUC365, Season 2 simulations performed for the fewer IC subjects in MUSIC seem to be enclosed within the predicted exposure ranges for the CHD and CLD subjects in MEDLEY that received a Season 2 treatment. It is noticeable that exposures seemed slightly higher in CLD subjects compared to CHD subjects and lowest in subjects with IC. For all subjects in MEDLEY that received a Season 2 dose (n=189), AUC365 ranged up to 41.9 day×mg/mL, which is almost twice the maximum exposure from studies D5290C00003, MELODY and MEDLEY Season 1.

Further simulations were carried out across the range of study weights/ages for a typical subject in virtual patients. For these simulations it was assumed Season 2 subjects did not receive a Season 1 dose. However, this is not reflecting the SmPC recommendations where there are no restrictions to receive a Season 2 dose for infants not undergoing cardiac surgery. The 200 mg dose results in exposures almost twice the approved 50 and 100 mg Season 1 doses. The 2nd dose also results in a lower CL than expected from age and weight.

Safety data was collected for subjects who received Season 2 treatment from MEDLEY and MUSIC. In MEDLEY RSV Season 2, a total of 6 subjects weighed < 7 kg on Day 1 of RSV Season 2, of which 5 received the projected Season 2 treatment. Treatment emergent AEs were reported for all 5 subjects. In MUSIC, only one subject weighed <7 kg on Day 1 of RSV Season 2. The Applicant provided Day 31 and Day 151 Season 2 serum concentrations from the 5 subjects in MEDLEY which ranged from 154.07 µg/mL to 251.30 µg/mL at Day 31 and from 1.8 µg/mL to 84.08 µg/mL at Day 151. This is well above the mean serum concentration of 153.96 µg/mL at Day 31 (Season 2). Tmax is at Day 8. Thus, it can be concluded that the 5 subjects with a body weight <7 kg who received a Season 2 dose of 200 mg in the MEDLEY study, all experienced a higher than average exposure.

The exposure simulation based on extreme high body weight, defined as infants in Season 2 weighing ≥ 13 kg at the time of dosing, indicated that the Day 151 serum concentration would be within the exposure range of MELODY Season 1 and the Dose 2 AUC0-365 most likely be above the target AUC of 12.8 day·mg/mL previous identified as the efficacy threshold for optimal protection.

The Season 2 dose gave rise to higher exposures in most subjects than the approved Season 1 treatment.

Update of nirsevimab PK-parameters from the updated pop-PK analysis.

Absorption

The bioavailability (F) and absorption rate constant (ka) after IM administration of nirsevimab were determined to 84% in and 0.401 day-1 in the updated pop-PK analysis. This corresponds to an absorption t1/2 of 1.7 days. It should be noted that these data are defined on adult data but are assumed to be the same in infants.

Distribution

In the updated pop-PK analysis, the central and peripheral volume (Vc and Vp) of nirsevimab, for an infant weighing 5 kg (11.1 months postmenstrual age), were determined to 216 ml and 261 ml, respectively. The distribution clearance Q was determined to 150 mL/day in new pop-PK model.

Elimination

The clearance CL for an infant weighing 5 kg (11.1 months postmenstrual age) was determined to 3.42 ml/day in the updated pop-PK analysis. The predicted mean (SD) terminal elimination half-life in infants was 71.4 (11.4) days.

Interindividual variability

From the updated popPK model interindividual variabilities (%CV) were determined of clearance Cl, central volumes, and absorption rate constant ka to 26%, 43% and 44%, respectively.

Dose proportionality and time dependencies

NA

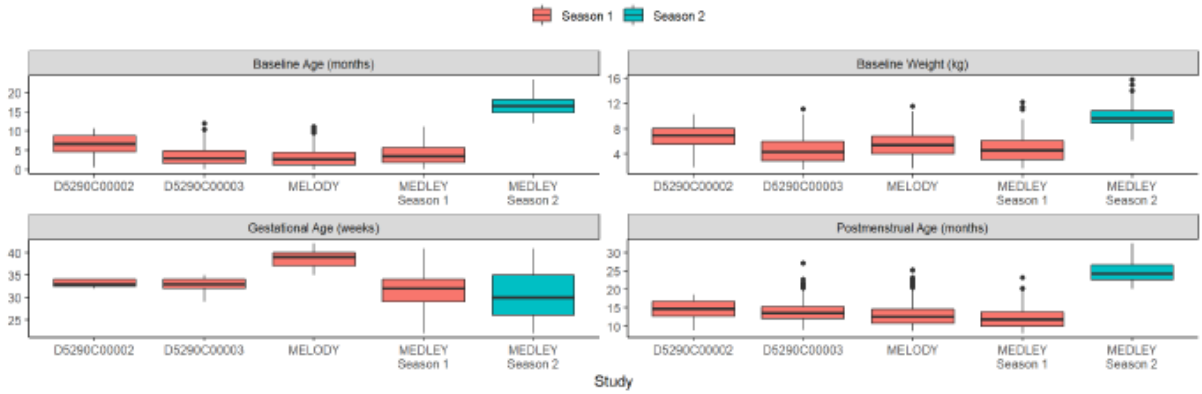
Special populations

The previously described popPK model includes the covariates body weight, postmenstrual age, race, and ADA status. An updated popPK model including additional data available from the MEDLEY and MELODY clinical studies was applied to reanalyse the covariates Race and ADA status impact on nirsevimab's PK. Race and ADA status were still found as significant covariates.

Body weight and postmenstrual age

The mean postmenstrual age and body weight as expected was higher in RSV season 2, see box-plot in of covariates in figure 12 below.

Figure 12 **Study Versus Continuous Covariate**



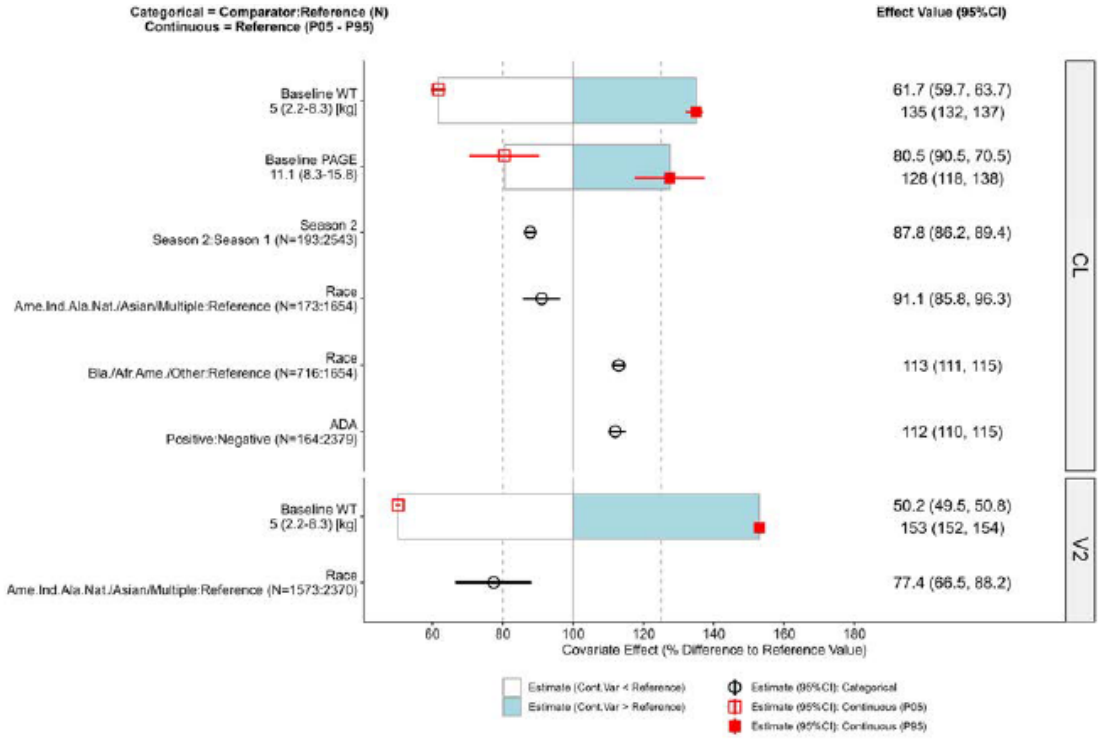
Source: ASTR-CP-2207-MEDI8897-bla-EDA-plots-music-22Jul2022.Rmd

Body weight remains the most important covariate in updated pop-PK model, scaling PK parameters from adults to infants, with updated estimated allometric exponents of 0.589 and 0.840 for clearances and volumes, respectively. Clearance in infants weighing 2.2 kg and 8.3 kg were predicted in the updated model to be 61.7% and 135%, respectively, of the CL in a 5 kg infant. The volume of distribution in infants weighing 2.2 kg and 8.3 kg were 50.2% and 153% of that of a 5 kg infant.

In addition to body weight, an effect of postmenstrual age is included to describe the clearance CL in infants, see figure 13 below.

Table 6

Forest Plot of Covariate Effects on CL and Volume of Distribution in Paediatric Subjects for the Final Population PK Model



Vertical dashed lines are the range of effect considered to be clinically insignificant. Reference race = White or Native Hawaiian/Pacific Islander.

ADA = anti-drug antibody; Ame.Ind./Ala.Nat .= American Indian or Alaskan Native; Bla./Afr.Ame.= Black or African American; CI = confidence interval; CL = clearance; Cont. Var = continuous variable; N = number of subjects with available information; P05 = 5th percentile; P95 = 95th percentile; PAGE = postmenstrual age; PK = pharmacokinetics; V2 = Vc = central volume; WT = body weight.

Source: Figure 10, 2022 Population PK report, Module 5.3.3.5, this Variation.

Simulations on basis of pop-PK model were performed to predict nirsevimab exposures for a 50 mg dose down to a body weight of 1 kg at the time of dosing, and a 200 mg dose in Season 2 down to 6.5 kg, see table 12 below. The lowest weight simulated subjects in Season 2 (6.5 kg) were predicted to have ~39% higher Cmax, ~85% higher concentrations at Day 150, and ~68% higher AUC0-365 than a 5 kg infant receiving 100mg. For all 3 infant doses, AUC0-365 and Cmax are predicted to be lower than the exposure observed for the highest dose tested in adults (3000mg IV), see Table 7 below. Predicted exposures following a 200 mg dose in Season 2 were within the range of safe and efficacious exposures.

Table 7 **Median-Predicted Exposures for Lowest Weight Subjects per Dose and Adult Maximum Dose**

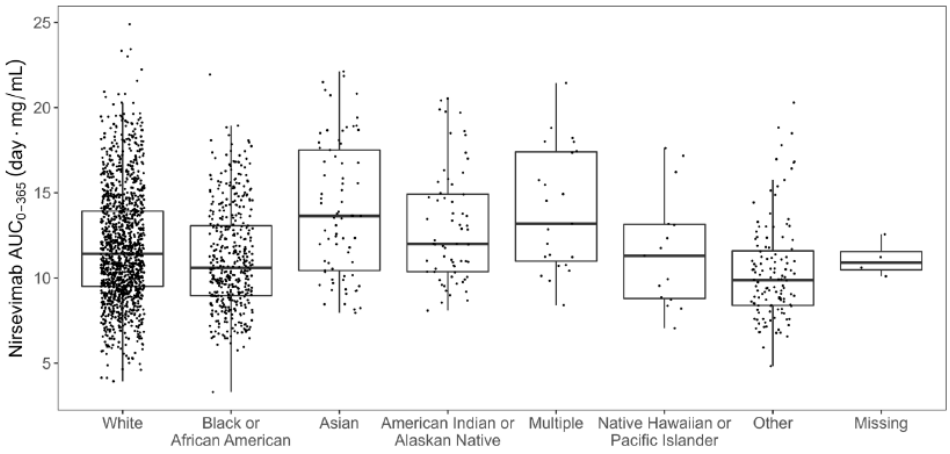
Exposure Metric	50 mg IM (1 kg infant)	100 mg IM (5 kg infant)	200 mg IM (6.5 kg child)	3000 mg IV (Adult Phase I)
$AUC_{baseline\ CL}$ (day•mg/mL)	70.8	29.1	41.9	59.5
$AUC_{0\text{-}365}$ (day•mg/mL)	19.7	15.8	26.6	57.0
C_{max} (ug/mL)	294	160	223	1140
Day 151 concentration (ug/mL)	33.0	36.3	67.2	NA
Day 365 concentration (ug/mL)	4.29	4.66	9.21	NA

Source: medi8897-sims-bla-08Aug2022.R
Notes: Pediatric data (50 mg, 100 mg, and 200 mg) are based on simulated population at the corresponding lowest weights (1 kg, 5 kg, and 6.5 kg). Adult data is based on post hoc predictions from the final model for subjects in study D5290C00001.
Abbreviations: $AUC_{0\text{-}365}$=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; $AUC_{baseline\ CL}$=area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetic model; C_{max}=maximum predicted concentration derived from post hoc clearance values at dosing from the final population pharmacokinetic model; IM=intramuscular; IV=intravenous; NA=not applicable

Race

Races were re-grouped in the updated pop-PK analysis, since some of the estimated race effects in the previous model were small and uncertain. The conclusion has not changed: predicted exposures per race group indicated no clinically relevant differences between race groups, see boxplots in figure 14 below.

Figure 14 **Boxplots of $AUC_{0\text{-}365}$ vs Race for the Final PopPK Model**



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443)
Notes: Black dots are individual posthoc predictions for pediatric subjects from Studies D5290C00003, MELODY, and MEDLEY with weight <5kg receiving 50mg, weight ≥5kg receiving 100mg in Season 1.
Abbreviations: $AUC_{0\text{-}365}$=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; popPK=population pharmacokinetic.

The final population PK model included effects of race on CL and central volume (Vc), as they provided significant improvement to the model fit. However, the estimated effects were generally small (< 20%), and therefore have no clinically relevant impact on exposure.

PK data - MEDLEY RSV season 2 and MUSIC season 1 and 2

MEDLEY study (D5290C00005). Evaluation of nirsevimab PK in CHD and CLD patients in their second RSV season

Overview of MEDLEY study design - RSV Season 2

MEDLEY is an ongoing, randomised, double-blind, palivizumab-controlled study designed to evaluate the safety, PK, ADA response, and descriptive efficacy of nirsevimab in high-risk infants eligible to receive palivizumab when entering their first or second RSV season.

In RSV Season 2, subjects received either a single dose of 200 mg IM nirsevimab followed by 4 once-monthly IM doses of placebo, or 5 once-monthly IM doses of 15 mg/kg palivizumab, per randomisation. Subjects from the CLD/CHD cohort who were randomised to nirsevimab in RSV Season 1 received a second dose of nirsevimab in Season 2 (NIRS/NIRS treatment group; n = 180 subjects). Eighty-two subjects from the CLD/CHD cohort who were randomised to palivizumab in Season 1 were re-randomised 1:1 to palivizumab (PALI/PALI treatment group; n = 42) or nirsevimab (PALI/NIRS treatment group; n = 40) in RSV Season 2. Enrolment is complete and the RSV Season 2 Analysis (data cut-off 30 April 2022) was triggered after all subjects from the CLD/CHD cohort had completed follow-up through the second 5-month RSV season (i.e, Season 2 Day 151 visit) and also included all available Season 1 data (through Day 361) and Season 2 (through at least Day 151) safety, efficacy, PK, and ADA data at the time of the data cut-off. The updated MEDLEY iCSR (dated 31 August 2022) submitted with this variation includes all available data for RSV Season 1 and Season 2.

Pharmacokinetics of nirsevimab in MEDLEY study RSV Season 2

The serum concentration of nirsevimab in the MEDLEY study was determined using a sparse PK-sampling scheme with minimum 3 timepoints (Day 8 (few Japanese subjects) Day 15/31, Day 151 and Day361), see table 7 below.

Table 8 **Summary of Nirsevimab Serum Concentrations (µg/mL) by Scheduled Sampling Time Through at least 150 Days Post First Dose in Season 2 for 200 mg Fixed Dose – As-treated Population (Season 2)**

Summary statistic	Scheduled time					
	Baseline	Day 8	Day 15	Day 31	Day 151	Day 361
Subjects with CLD/CHD (N = 220)						
n	168	11	97	108	192	79
n < LLOQ	24	0	3	4	5	9
Arithmetic Mean	3.30	260.11	179.84	153.96	52.27	6.65
Arithmetic SD	2.73	49.23	64.44	71.96	24.92	4.90
Geometric Mean	2.31	256.01	136.33	94.79	41.29	4.60
Geometric CV%	113.5	18.8	195.1	347.3	126.9	135.8

The LLOQ for nirsevimab is 0.5 µg/mL.
Geometric mean – gSD=exp(mean(log(PK Conc)) – SD(log(PK Conc))).
Geometric mean + gSD=exp(mean(log(PK Conc)) + SD(log(PK Conc))).
Geometric mean and other stats were derived from planned visit day ± 14 days.
Subjects redosed after heart surgery (n = 2 in Season 2) were included (see Table 14.1.3.2).

PK-parameters were predicted post. hoc. for the MEDLEY study using the final population PK model and the parameters were compared with the pivotal MELODY study, see table 8. Furthermore,

measured serum concentrations at Day 151 in the MEDLEY study RSV season 2 was compared with MELODY and MEDLEY RSV season 1, see table 9.

Table 9 Summary of Post Hoc Predicted PK Parameters for the Final popPK Model

Parameter		**D5290C00003 (N = 542)**	**MELODY (N = 954)**	**MEDLEY Season 1 (N = 590)**	**MEDLEY Season 2 (N = 189)**	**Total (N = 2275)**
Clearance at dosing (mL/day)	Mean (SD)	2.52 (0.781)	4.03 (1.80)	3.40 (1.61)	7.46 (2.64)	3.79 (2.08)
	Median [min, max]	2.43 [1.21, 6.05]	3.65 [1.03, 19.4]	3.09 [1.19, 14.3]	6.68 [3.31, 20.0]	3.27 [1.03, 20.0]
	Geo. mean (Geo. CV%, Geo. SD)	2.41 (30.8%, 1.35)	3.71 (41.3%, 1.49)	3.11 (43.4%, 1.51)	7.11 (30.4%, 1.35)	3.38 (49.4%, 1.60)
Total volume at dosing (mL)	Mean (SD)	332 (91.6)	519 (187)	450 (190)	860 (278)	485 (225)
	Median [min, max]	320 [170, 789]	492 [198, 1740]	425 [198, 2670]	794 [507, 2480]	439 [170, 2670]
	Geo. mean (Geo. CV%, Geo. SD)	320 (27.4%, 1.31)	491 (34.1%, 1.39)	421 (36.4%, 1.42)	830 (25.5%, 1.28)	445 (42.2%, 1.50)
Predicted terminal half-life (days)	Mean (SD)	71.0 (10.4)	70.7 (11.4)	72.9 (12.3)	71.2 (10.9)	71.4 (11.4)
	Median [min, max]	70.5 [34.6, 108]	70.7 [28.3, 148]	73.0 [31.2, 153]	73.2 [41.2, 103]	71.5 [28.3, 153]
	Geo. mean (Geo. CV%, Geo. SD)	70.2 (15.0%, 1.16)	69.8 (16.7%, 1.18)	71.9 (17.0%, 1.18)	70.3 (16.3%, 1.18)	70.5 (16.4%, 1.18)
Predicted C_{max} (µg/mL)	Mean (SD)	118 (29.2)	120 (28.0)	123 (27.1)	194 (42.2)	127 (35.9)
	Median [min, max]	115 [48.5, 205]	118 [40.9, 193]	123 [29.2, 190]	198 [64.1, 315]	122 [29.2, 315]
	Geo. mean (Geo. CV%, Geo. SD)	115 (25.5%, 1.29)	116 (25.0%, 1.28)	120 (24.2%, 1.27)	189 (25.5%, 1.28)	122 (28.5%, 1.32)
Predicted $AUC_{0\text{-}365}$ (day•mg/mL)	Mean (SD)	10.4 (2.17)	12.2 (3.55)	12.3 (3.34)	21.5 (5.52)	12.6 (4.44)
	Median [min, max]	10.2 [4.87, 17.2]	11.8 [3.31, 24.9]	11.8 [4.14, 23.4]	21.8 [7.45, 41.9]	11.6 [3.31, 41.9]
	Geo. mean (Geo. CV%, Geo. SD)	10.1 (21.7%, 1.24)	11.7 (30.6%, 1.35)	11.8 (28.4%, 1.32)	20.8 (28.9%, 1.33)	11.9 (33.7%, 1.39)

Table 10 Summary of Post Hoc Predicted PK Parameters for the Final popPK Model

Parameter		D5290C00003 (N = 542)	MELODY (N = 954)	MEDLEY Season 1 (N = 590)	MEDLEY Season 2 (N = 189)	Total (N = 2275)
$AUC_{baseline\ CL}$ (day•mg/mL)	Mean (SD)	21.7 (6.47)	21.3 (6.50)	22.6 (6.22)	29.5 (8.19)	22.4 (6.93)
	Median [min, max]	20.5 [8.27, 41.4]	20.4 [5.16, 48.7]	22.3 [6.98, 43.8]	30.0 [9.75, 60.4]	21.6 [5.16, 60.4]
	Geo. mean (Geo. CV%, Geo. SD)	20.7 (30.8%, 1.35)	20.4 (32.0%, 1.37)	21.7 (29.7%, 1.34)	28.3 (30.5%, 1.35)	21.4 (32.3%, 1.37)

Source: ASTR-NIRSE-run-plots-bla-Feb2023.R (run443)
Notes: Sixteen samples with |CWRES| >5 were removed in the final model. Only subjects pediatric subjects with weight <5kg receiving 50mg, weight ≥5kg receiving 100mg in Season 1, or subjects receiving 200mg in Season 2 are included.
Abbreviations: AUC0-365=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; AUCbaseline CL =area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final popPK model; C_{max}=maximum plasma concentration; CV=coefficient of variation; |CWRES| >5=the absolute value of the associated conditional weighted residual is greater than 5; geo.=geometric; max=maximum; min=minimum; N=number of subjects with available information; PK=pharmacokinetic; popPK=population PK; SD=standard deviation

Table 11 **Summary of Observed Day 151 Serum Concentrations in MEDLEY Subjects Compared to MELODY**

	N	Mean (SD)	Median (q25, q75)	Min, Max
MELODY	636	26.6 (11.1)	24.5 (18.5,34.1)	2.10, 76.6
MEDLEY: CHD Season 1	46	29.2 (13.3)	30.6 (17.5,41.5)	6.46, 51.3
MEDLEY: CLD Season 1	117	28.9 (10.9)	27.4 (20.7,35.8)	4.69, 66.2
MEDLEY: CHD Season 2	51	54.4 (21.7)	55.5 (42.3,64.5)	11.2, 106
MEDLEY: CLD Season 2	112	56.3 (23.3)	55.0 (43.7,68.0)	13.0, 189
MEDLEY: GA <29 weeks w/o CHD or CLD Season 1	39	27.5 (10.8)	28.4 (18.1,32.1)	12.1, 54.4
MEDLEY: GA ≥29 weeks w/o CHD or CLD Season 1	255	27.1 (10.8)	25.6 (19.4,33.4)	2.06, 62.6

Conc = concentration; CV% = percent coefficient of variation; exp = exponential; gSD = geometric standard deviation; LLOQ = lower limit of quantification; log = logarithm; PK = pharmacokinetics; NA = not applicable; SD = standard deviation.
Source: Table 14.5.1.1.2.

Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443)
Notes: Day 151 concentrations are Visit day 151 ± 14 days. Data presented are pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg in Season 1, and/or receiving 200mg in Season 2. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's syndrome) and was excluded for extrapolation.
Abbreviations: CHD=congenital heart disease; CLD=chronic lung disease; GA=gestational age; Max=maximum; ; Min=minimum; N=number of subjects with available information,q25=25th quartile, q75=75th quartile

PK-based extrapolation of efficacy in MEDLEY study (and MUSIC study)

MEDLEY evaluated the safety and PK of nirsevimab in a higher-risk (palivizumab-eligible) population. No formal hypothesis testing for efficacy was intended in MEDLEY. The efficacy of nirsevimab in this population was assessed by PK extrapolation, as agreed per Committee for Human Products for Medicinal Use advice. Efficacy was extrapolated to infants in their first RSV

season, including infants with CHD and CLD, in the MAA Data supporting extrapolation to children with CHD and CLD in their second RSV season are presented below.

Extrapolation plan

The plan for extrapolation of efficacy to children who remain vulnerable to severe RSV disease entering their second season relies on the same assumptions as for infants in their first season:

- Comparable viral aetiology between the paediatric populations healthy preterm and term infants, and the higher-risk populations (MEDLEY, MUSIC).
- 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 concentrationand RSV-neutralising ability across all subgroups. Similar expected safety across subgroups since nirsevimab does not bind to any endogenous target.

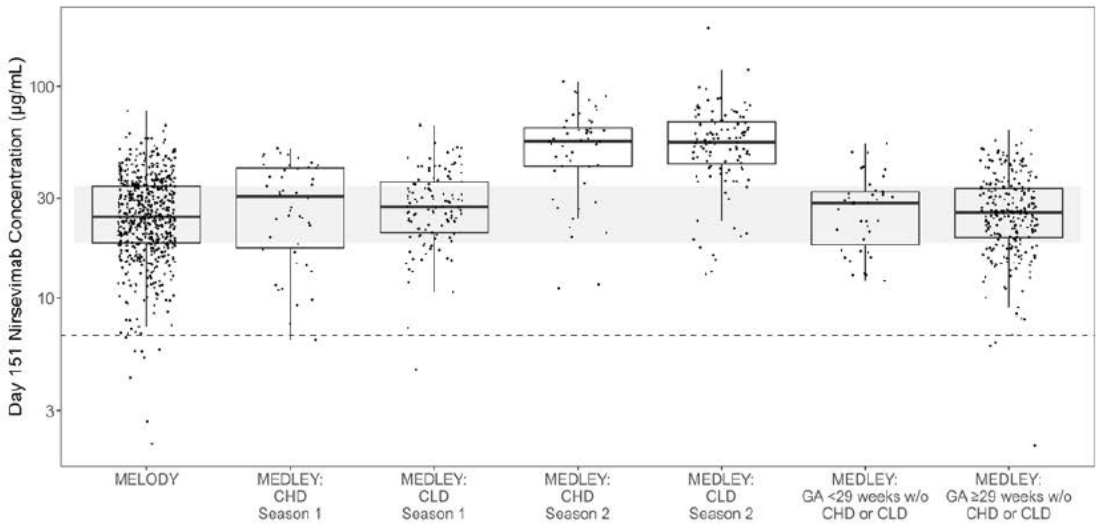
Extrapolation was performed applying 2 approaches: 1) comparison of observed nirsevimab serum concentrations at Day 151 in the MEDLEY study (and MUSIC) to those in the MELODY study; 2) comparison of derived exposures in MEDLEY (and MUSIC) to the efficacy exposure target (per the agreed paediatric investigation plan). The first approach is not model-dependent and therefore relies on fewer assumptions. The second approach included derivation of individual nirsevimab exposures in MEDLEY (and MUSIC) from the final population PK model. Efficacy was considered to be demonstrated if the proposed doses resulted in serum nirsevimab exposures at or above the predicted efficacious target, based on exposure-response analysis, in > 80% of the MEDLEY population (as agree with Committee for Human Products for Medicinal Use). AUCbaselineCL was selected as the main metric for exposure-response analyses and subsequently extrapolation because CL at baseline can be fairly robustly derived based on the sparse sampling schedule, without assumptions of the growth rate of the child as for AUC0-365.

PK extrapolation analysis

Nirsevimab serum concentrations at Day 151 for the MEDLEY subgroups and MELODY subjects are visualised in Figure 15 below. Serum concentrations on Day 151 of Season 2 in children with CHD and CLD were slightly higher than those in healthy infants. Based on the extrapolation plan agreed in the paediatric investigation plan, extrapolation of efficacy was demonstrated in the overall MEDLEY population in Season 2, as nirsevimab exposures were above the efficacious target (i.e, AUCbaselineCL 12.8 mg·day/mL) in overall 98.4% (187/190) of the children; 97.7% (129/132) in the CLD cohort, and in 100% (58/58) in the CHD cohort.

Figure 15

Boxplots of Observed Day 151 Serum Concentrations in MEDLEY Subjects Compared to MELODY



Day 151 concentrations are Visit Day 151 ± 14 days. Grey band is the reference inter-quartile range for MELODY Day 151. The horizontal dashed black line is the nonclinical EC90 (6.8 µg/mL). Data presented are paediatric subjects who are < 5 kg receiving 50 mg, ≥ 5 kg receiving 100 mg in Season 1, and/or receiving 200 mg in Season 2. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's syndrome) and was excluded for extrapolation. The 2 groups on the right, MEDLEY: GA < 29 weeks without CHD or CLD and MEDLEY: GA ≥ 29 weeks without CHD or CLD, contain only Season 1 subjects.

CHD = congenital heart disease; CLD = chronic lung disease; EC90 = 90% effective concentration; GA = gestational age.

Source: Figure 28, 2022 Population PK report. Module 5.3.3.5, this Variation.

Table 12 Extrapolation Results for Pediatric Season 2 Subjects in MEDLEY Stratified by CHK/CLD Status

	CHD (N=58)	CLD (N=132)	Total (N=190)
$AUC_{baseline\ CL} \geq$ Target	58 (100%)	129 (97.7%)	187 (98.4%)
$AUC_{baseline\ CL} <$ Target	0 (0%)	3 (2.3%)	3 (1.6%)

Source: ASTR-NIRSE-run-plots-bla-Feb2023.R (run443)

Notes: The target exposure 12.8 day·mg/mL, CHD group includes 9 subjects with CHD/CLD. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's Syndrome) and was excluded for extrapolation.

Abbreviations: $AUC_{baseline\ CL}$ =area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model; CHD=congenital heart disease; CL=clearance; CLD=chronic lung disease; N=number of subjects with available information

No statistically significant effect of CHD or CLD on nirsevimab PK was found, further supporting similar exposures across subgroups. Based on these results, children in the MEDLEY subgroups achieved comparable serum exposures to the healthy infant population in which efficacy was established, supporting a single 200 mg IM dose of nirsevimab in Season 2 for prevention of RSV lower respiratory tract disease in children < 24 months with CLD of prematurity or haemodynamically significant CHD in their second RSV season.

In the part of the MEDLEY study (D5290C00005) submitted in the current variation, nirsevimab was evaluated in CLD and CHD children (n=220) below 2 years in their second RSV season. An IM dose of 200 mg nirsevimab was administered to 180 children in their second RSV season which had previously received nirsevimab in the first RSV season and 40 children which had previously received palivizumab in the first RSV season. PK and immunogenicity were evaluated in the study. Efficacy was extrapolated on basis of PK, according to PIP. A sparse PK-sampling scheme in the MEDLEY study of minimum 4 timepoints (Baseline, Day 15/31, Day 151 and Day361) for each subject was comparable to sampling in the MELODY study.

In the MEDLEY study, RSV season 2, it was demonstrated that nirsevimab' s mean serum concentration in CHD and CLD patients at day 151 (54.4 and 56.3 µg/mL) was similar and that it was considerable higher, approximately 1.8-fold higher, than in the MEDLEY study, RSV season 1 and in the pivotal MELODY study. It was shown that nearly all subjects serum concentration at day 151 was above the preclinical determined EC90 value of 6.8 µg/ml. It was demonstrated that the post hoc. predicted exposure mean-AUCbaselineCl in RSV season 2 (29.5 day*mg/mL) was also higher, approximately 1.4-fold, than in MELODY study. Mean baseline concentration was negligible (2-3 µg/mL), showing that the higher exposure in season 2 is not due to accumulation. The increased exposure in RSV season 2 could potentially influence the safety profile, though it was also shown by the Applicant that the higher mean exposure was below an exposure in adults (59.5 day*mg/mL, 3000 mg IV dose) that is considered as safe.

The efficacy of nirsevimab in CLD and CHD children in RSV season 2 was assessed by PK extrapolation according to PIP. It was demonstrated that nirsevimab exposures were above the efficacious target level (i.e., AUCbaselineCL 12.8 mg·day/mL) in overall 98.4% (187/190) of the children.

In conclusion, the Applicant has demonstrated that a 200 mg IM dose of nirsevimab is suitable for protecting children with CLD and CHD children in their second RSV season.

MUSIC study: Evaluation of nirsevimab in immunocompromised children in their first and second RSV season:

Study design: MUSIC was a Phase II, open-label, uncontrolled single-dose study to assess the safety and tolerability, PK, occurrence of ADA, and descriptive efficacy of nirsevimab in immunocompromised children who were ≤ 24 months of age at the time of dose administration. Approximately 50 subjects entering their first RSV season were to receive nirsevimab as a single, fixed IM dose of 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg. Approximately 50 subjects entering their second RSV season were to receive nirsevimab as a single, fixed IM dose of 200 mg. All available PK, ADA, and serology data through Day 361 in either RSV Season 1 or Season 2 were analysed and included in this submission.

Pharmacokinetics of nirsevimab in MUSIC study RSV season 1 and 2

The serum concentration of nirsevimab in the MUSIC study was determined using a sparse PK-sampling scheme with minimum 3 timepoints (Day 8 (few Japanese subjects) Day 15/31, Day 151 and Day361), see table 12 below.

Table 13 **Summary of Serum Concentrations (µg/mL) of Nirsevimab (As-treated Population)**

Summary statistic	Scheduled visit				
	Baseline	Day 8 [a]	Day 31	Day 151	Day 361
Nirsevimab 50 mg/100 mg (N = 48)					
n	48	15	47	39	29
n <LLOQ	48	0	1	1	7
Geometric mean	NQ	139.24	66.00	19.80	1.86
Geometric CV (%)	NC	22.26	141.06	101.19	119.96
Arithmetic mean	NQ	142.41	84.34	24.71	2.76
Arithmetic SD	NC	31.17	36.67	13.77	2.52
Nirsevimab 200 mg (N = 52)					
n	52	11	50	44	38
n <LLOQ	51	0	0	0	10
Geometric mean	NC	206.79	109.77	24.14	1.93
Geometric CV (%)	NC	16.58	91.74	121.54	158.95
Arithmetic mean	NC	209.35	131.22	32.56	3.46
Arithmetic SD	NC	34.35	56.82	19.10	3.91

[a] Day 8 data was only collected for Japanese subjects.

Geometric mean and other statistics were derived from planned visit day ± 14 days.

CV = coefficient of variation; LLOQ = lower limit of quantification (0.5 µg/mL); N = number of subjects as per actual dose administered; n= number of subjects in analysis; NA = not applicable; NC = not calculated; NQ = non-quantifiable; PK = pharmacokinetics; SD = standard deviation.

Source: Table 14.4.1.1_a.

PK-parameters were predicted post. hoc. for the MUSIC study using the final population PK model and the selected parameters were compared with the pivotal MELODY study, see table 2. Measured serum concentrations at Day 151 in the MUSIC study RSV season 2 was compared with MELODY and MEDLEY, see table 13. Furthermore, the exposure AUCbaselinecl and serum concentration at day 151 were compared between season 1 and 2, see table 13 and figure 16 and 17.

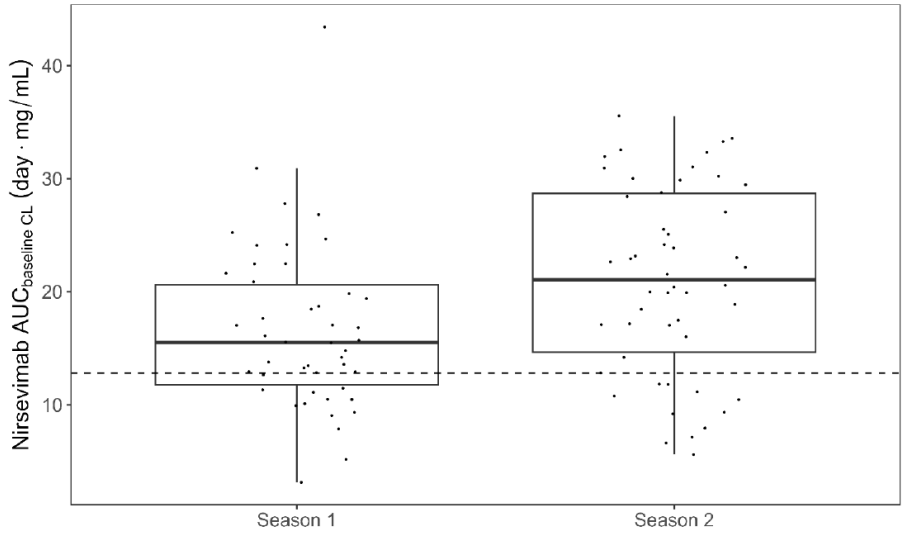
Table 14 **Nirsevimab IM Dose Exposures in MELODY and MUSIC**

Study/Season	N for AUC values	Mean $AUC_{0\text{-}365}$ (SD) [range], mg × day/mL	Mean $AUC_{baseline\ CL}$ (SD) [range], mg × day/mL	N for Day 151 serum concentration values	Mean Day 151 (± 14 days) serum concentration (SD) [range], µg/mL
MELODY (Primary Cohort)	954	12.2 (3.5) [3.3-24.9]	21.3 (6.5) [5.2-48.7]	636	26.6 (11.1) [2.1-76.6]
MUSIC/ Season 1	46	11.2 (4.3) [1.2-24.6]	16.7 (7.3) [3.1-43.4]	37	25.6 (13.4) [5.1-67.4]
MUSIC/ Season 2	50	16 (6.3) [2.2-25.5]	21 (8.4) [5.6-35.5]	42	33.2 (19.3) [0.9-68.5]

$AUC_{0\text{-}365}$= area under the concentration-time curve from 0 to 365 days post dose; $AUC_{baseline\ CL}$ = area under the serum concentration-time curve derived from post hoc clearance values at dosing; IM = intramuscular; PK = pharmacokinetic(s).

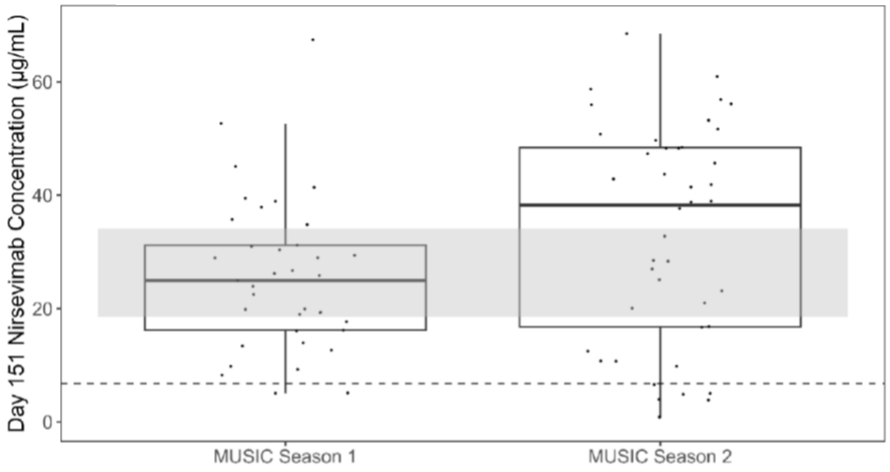
Source: Based on individual population PK parameters reported in the 2022 population PK report, Module 5.3.3.5, and the 2023 population PK report Addendum, Module 5.3.3.5.

Figure 16 **Boxplots of $AUC_{baseline\ CL}$ for MUSIC Subjects Grouped by Season**



Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)
Notes: The horizontal dashed black line is the target exposure (12.8 day·mg/mL). Subjects 4305001 and 7005002 (MUSIC) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.
Abbreviations: $AUC_{baseline\ CL}$=area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model

Figure 17 **Boxplots of Observed Day 151 Serum Concentrations MUSIC Subjects Compared to MELODY**

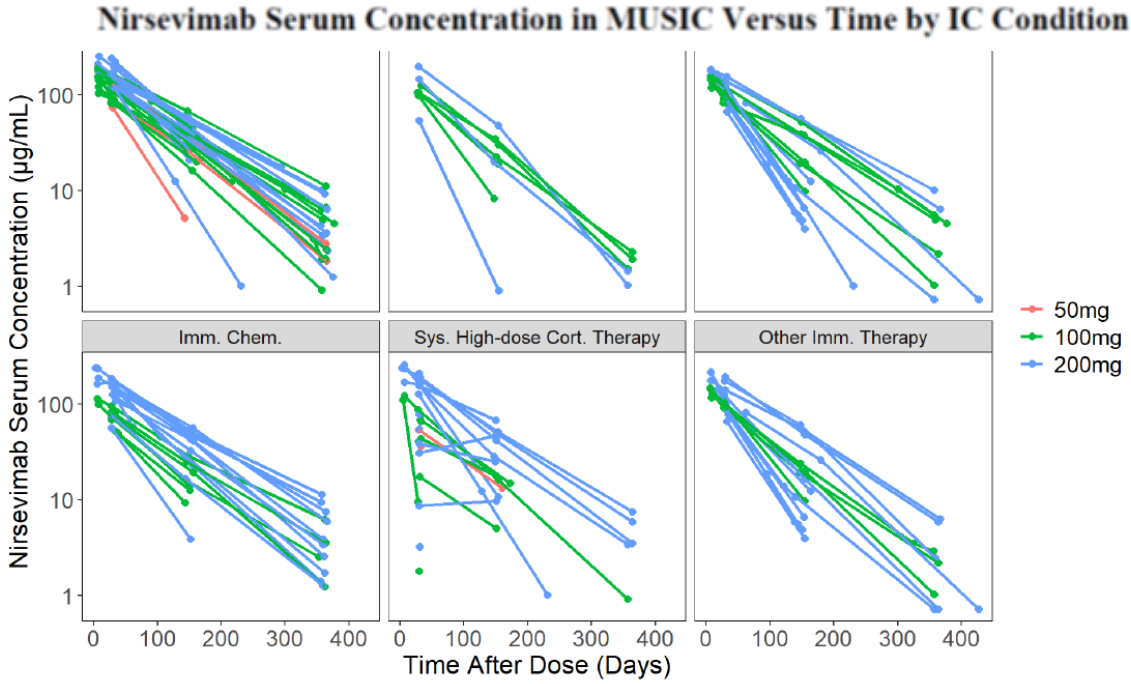


Source: ASTR-NIRSE-run-plots-bla-MUSIC-May2023.R (run600)
Notes: Day 151 concentrations are Visit day 151 ± 14 days. Grey band is the reference inter-quartile range for MELODY Day 151 concentrations. The horizontal dashed black line is the *preclinical* EC90 (6.8 µg/mL). Subjects 4305001 and 7005002 (MUSIC) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; Day 151 concentrations were 52.6µg/mL and 23.9 µg/mL, respectively. Data presented are pediatric subjects who are <5kg receiving 50mg or ≥5kg receiving 100mg in Season 1 or receiving 200mg in Season 2.
Abbreviations: EC90=90% effective concentration

PK in different subgroups of immunocompromised children

Individual nirsevimab serum concentrations versus time in MUSIC are shown by IC condition in Figure 18.

Figure 18



Source: ASTR-CP-2207-MEDI8897-EDA-RegQuestions-May2023.Rmd, ASTR-CP-2207-MEDI8897-EDA-RegQuestions-May2023.html

Notes: Subjects with more than one qualifying IC condition appear in multiple panels.

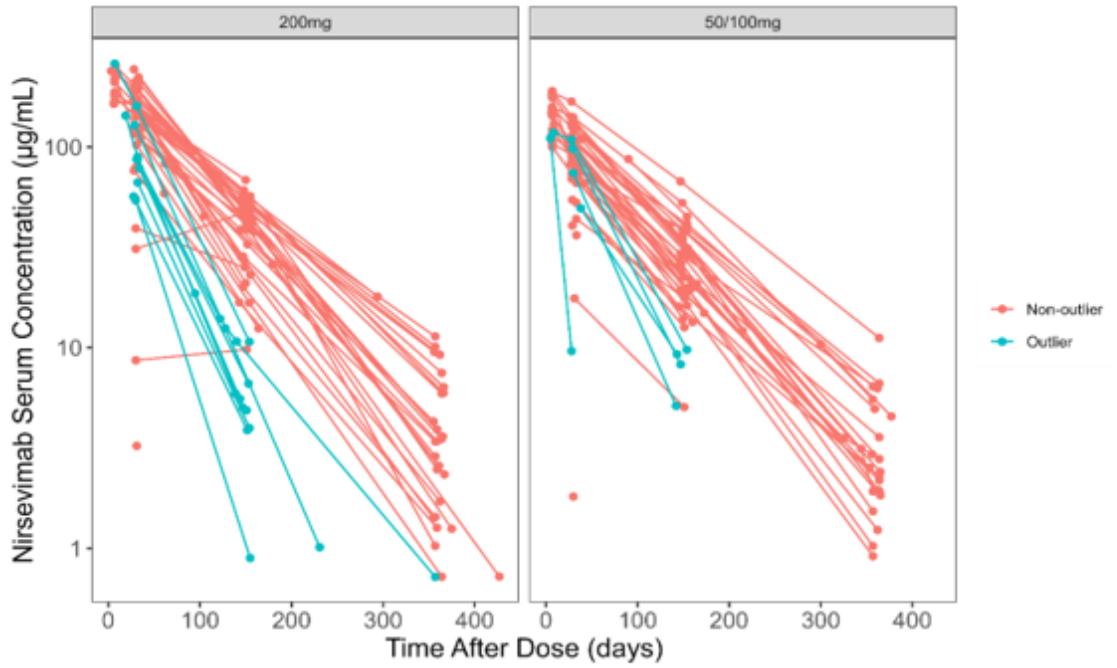
Abbreviations: Comb./Ant./Other Imm.=combined immunodeficiency, antibody deficiency, other immunosuppressive therapy; Human Imm. Virus Inf.= diagnosed with human immunodeficiency virus infection; IC=immunocompromised; Imm. Chem.= subject is receiving immunosuppressive chemotherapy; Organ or Bone Mar. Trans.= history of organ or bone marrow transplantation; Sys. High-dose Cort. Therapy= subject is receiving systemic high-dose corticosteroid therapy; Other Imm. Therapy= subject is receiving other immunosuppressive therapy

Analysis of PK outlier in MUSIC study

In the immunocompromised children in MUSIC, there were 14 outliers with more rapid decline in serum concentration-time profiles identified, see figure 19. Extensive medical review found evidence of protein losing conditions (nephrotic syndrome or protein-losing enteropathy) in these subjects, which was suspected to influence the PK of nirsevimab (Protein-losing conditions may lead to hypogammaglobulinaemia (Otani et al, 2022). The principal mechanisms of protein loss are nephrotic syndrome and PLE. Protein losing enteropathies may result from the presence of mucosal injury due to erosive or ulcerative gastrointestinal disorders (enabling inflammatory exudates to cross the compromised epithelium), increased mucosal permeability due to compromised mucosal integrity (allowing protein to leak into the lumen), and intestinal loss of lymphatic fluid secondary to lymphatic obstruction. Chronic liver disease with cirrhosis, portal hypertension, or hepatic venous outflow obstruction, may be associated with intestinal lymphangiectasia and PLE.

Figure 19

Individual Concentration vs Time Profiles for Immunocompromised Subjects (MUSIC) with Outliers Highlighted



Dots are individual data points for subjects from MUSIC. Blue indicates subjects identified as outliers with increased clearance. Red indicates subjects not identified as outliers.

Source: Figure 9, 2023 population PK report addendum.

Clinical Conditions Potentially Associated with Protein Loss

A subset of immunocompromised subjects (14/96) had increased clearance of nirsevimab. (Table 14). Their medical histories have been reviewed to identify potential causes. One subject had nephrotic syndrome, in which glomerular damage leads to heavy proteinuria. Two subjects had GVH disease. In GVH disease the immunological attack can damage the integrity of the mucosa and cause protein losing enteropathy. Five subjects had chronic liver disease with cirrhosis, portal hypertension, or hepatic venous outflow obstruction which through the formation of secondary intestinal lymphangiectasia leads to a protein losing enteropathy. Two subjects had Omenn syndrome, a rare disease, with the clinical features of severe erythroderma and protracted diarrhoea that are associated with protein loss from both the skin and the gut (Villa et al 2008) (Note that one subject with Omenn syndrome and GVH disease is counted twice). Two subjects had HIV infection. Mechanisms by which HIV infection can lead to urinary and gastrointestinal protein loss include the virus directly attacking the kidneys and the gastrointestinal tract, opportunistic enteric infections causing recurrent and chronic diarrhoea, or renal toxicity from anti-retroviral therapy (Otani et al 2022). The 3 remaining subjects had malignancies of congenital retinoblastoma, choroid plexus carcinoma, and juvenile myelomonocytic leukaemia. Proteolytic degradation, the primary elimination pathway of mAbs, can be increased and induced by ongoing systemic inflammation that is often a consequence of chronic diseases such as malignancies (Ryman et al 2017).

Table 15 **Subjects with Increased Clearance in MUSIC (N = 14)**

Subject	Clinical condition
0501001	Chronic liver disease
0501003	Chronic liver disease
0501004	Chronic liver disease
0501005	Chronic liver disease
4306004	Malignancy: Juvenile myelomonocytic leukaemia
4309001	Nephrotic syndrome
4311001	Chronic liver disease
6901005	HIV
6903002	Malignancy: Congenital retinoblastoma
6903009	HIV
7004005	Omenn syndrome
7801002	Malignancy: Choroid plexus carcinoma
7807002	GVH disease and Omenn Syndrome
7807003	GVH disease

GVH = graft versus host; HIV = human immunodeficiency virus.

Source: AstraZeneca analysis of MUSIC data.

A further evaluation was performed to see if those patients at risk of increased clearance of nirsevimab can be predicted in the nirsevimab data set. The frequency of the conditions known to be associated with protein loss in children with increased clearance were compared to the complete enrolment in the MUSIC study. The MedDRA preferred term alone was not sufficiently specific for differentiating subjects who had increased clearance from those with clearance in the expected range (Table 15). The analysis was limited by the information that was routinely recorded in the database. In particular, the precise extent of protein loss in individual subjects was not recorded. Potential markers such as serum albumin or immunoglobulin levels might have been predictive of which subjects will have had increased clearance. Although, interpretation of these readouts can be challenging in the immunocompromised population as it is difficult to know whether the underlying cause of low levels is decreased synthesis of protein or increased loss. These parameters were not collected in the MUSIC study and there are no blood sample reserves to investigate further.

The results of the MUSIC study have highlighted that children with protein losing conditions can have increased clearance of nirsevimab and that protein losing conditions occur more frequently in the immunocompromised population.

Table 16 **Clearance Categorisation for Subjects from MUSIC with Conditions Potentially Associated with Protein Loss (44/100 Subjects in Total)**

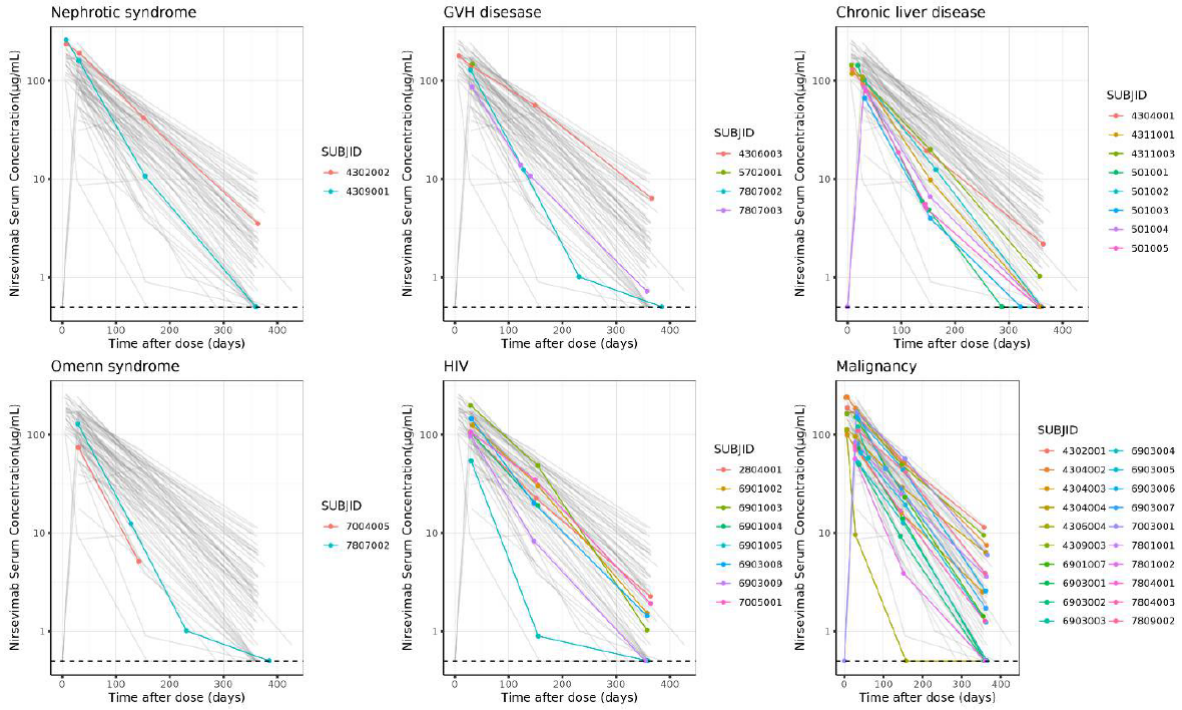
Protein losing condition (total number of subjects)	Number of subjects with increased clearance up to Day 151	Number of subjects with clearance in the expected range up to Day 151	Number of subjects with incomplete clearance data up to Day 151
Nephrotic syndrome (n = 2)	1	1	0
GVH disease (n = 4) [a]	2	1	1
Chronic liver disease (n = 8)	5	3	0
Omenn syndrome (n = 2) [a]	2	0	0
HIV (n = 8)	2	6	0
Malignancy (n = 21)	3	18	0

[a] One subject (Subject 7807002) had both GVH disease and Omenn syndrome.

GVH = graft versus host; HIV = human immunodeficiency virus.

Source: AstraZeneca analysis of MUSIC data.

Figure 20 **Nirsevimab Serum Concentrations over Time after Dosing in MUSIC**



Nirsevimab was the only IP administered in MUSIC.

Serum concentration over time data are available for 96 of 100 subjects who were administered a single dose of nirsevimab in MUSIC. Each line represents a single subject who was administered nirsevimab. Coloured lines represent subjects with the condition indicated above each plot. Grey lines represent subjects without the condition indicated above each plot. Subjects might have more than one condition. The black dashed line represents the lower limit of quantification.

One child (Subject 7807002) had both GVH disease and Omenn syndrome.

IP = investigational product; GVH = graft versus host; HIV = human immunodeficiency virus; SUBJID = subject identification.

Source: AstraZeneca analysis of MUSIC data.

PK-extrapolation of efficacy and safety in MUSIC study

The efficacy of nirsevimab in the population of immunocompromised children in their first or second RSV season in MUSIC, was extrapolated based on comparable PK, using similar methodology as agreed with the CHMP for the pivotal Phase II/III MEDLEY (Study D5290C00005) population of preterm infants and children with congenital heart disease / chronic lung disease in their first or second RSV season.

Extrapolation was performed using 2 complementary approaches: (i) comparison of nirsevimab serum concentrations at Day 151 (ie, corresponding to the length of a typical RSV season) in MUSIC to those in MELODY, and (ii) comparison of derived exposures in these studies to the efficacy exposure target, defined based on exposure-response analysis of pooled data from pivotal Phase IIb Study 3 (Study D5290C00003) and MELODY (Primary Cohort) (per the agreed Paediatric Investigation Plan in the EU). The pre-defined criterion for extrapolation was > 80% of subjects achieving nirsevimab exposures ≥ the efficacy exposure target (AUCbaseline CL of 12.8 mg × day/mL).

In MUSIC RSV Season 1 or 2, serum concentrations at Day 151 were overall comparable to those in MELODY, figure 21 page 48. The efficacy exposure target (AUCbaseline CL of 12.8 mg × day/mL) was met by 75.0% of subjects (71.7% [33/46] in Season 1 and 78.0% [39/50] in Season 2, see table 17 below).

Table 17 **Extrapolation Results for All Pediatric Subjects in MUSIC Stratified by Season**

	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)

Notes: The target exposure is 12.8 day·mg/mL. Subjects 4305001 and 7005002 (MUSIC) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.

Abbreviations: $AUC_{baseline\ CL}$ =area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model; N=number of subjects with available information

However, there was large between-subject variability in serum nirsevimab concentrations in MUSIC, with more rapid decline in serum concentrations over time observed in 14 subjects. These 14 subjects were considered outliers, see previous section for further details. After excluding these 14 subjects, 86.6% of subjects (80.5% [33/41] in Season 1 and 92.7% [38/41] in Season 2) achieved the target exposure associated with RSV protection, see table 17.

Table 18 **Extrapolation Results for All Pediatric Subjects in MUSIC Stratified by Season (outliers excluded)**

	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)

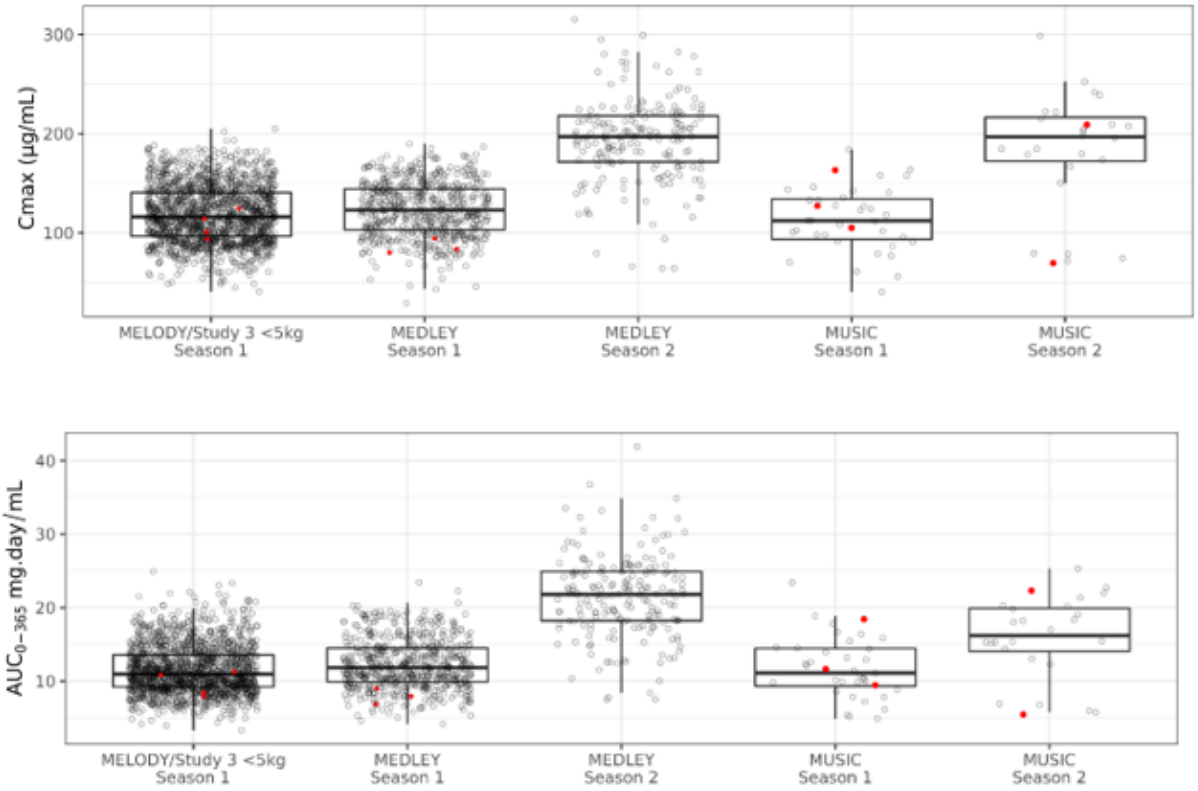
Notes: The target exposure is 12.8 day·mg/mL. Subjects 4305001 and 7005002 (MUSIC) were dosed 100mg at age 12.2 months (flagged as Season 2) but were included in Season 1 for extrapolation; both subjects had serum exposures above 12.8 day·mg/mL.

Abbreviations: $AUC_{baseline\ CL}$ =area under the serum concentration-time curve derived from post hoc clearance values at dosing from the final population pharmacokinetics model; N=number of subjects with available information

Exposure-safety analysis of MELODY, MEDLEY Season 1 and 2, and MUSIC Season 1 and 2

Boxplots of exposure-safety data from MELODY, MEDLEY Season 1 and 2, and MUSIC Season 1 and 2 do not indicate any relation of subjects with SAEs, and subjects with AESIs to Cmax or AUC0-365 (Figure X and Figure Y). There is no indication that SAEs or AESIs are exposure-dependent; exposures in subjects with SAEs or AESIs are spread across the ranges of exposures in the overall populations.

Figure X: Nirsevimab Exposure in MELODY, MEDLEY, and MUSIC Highlighting Subjects with at Least One AESI in Red; Cmax (Top), AUC0-365 (Bottom)

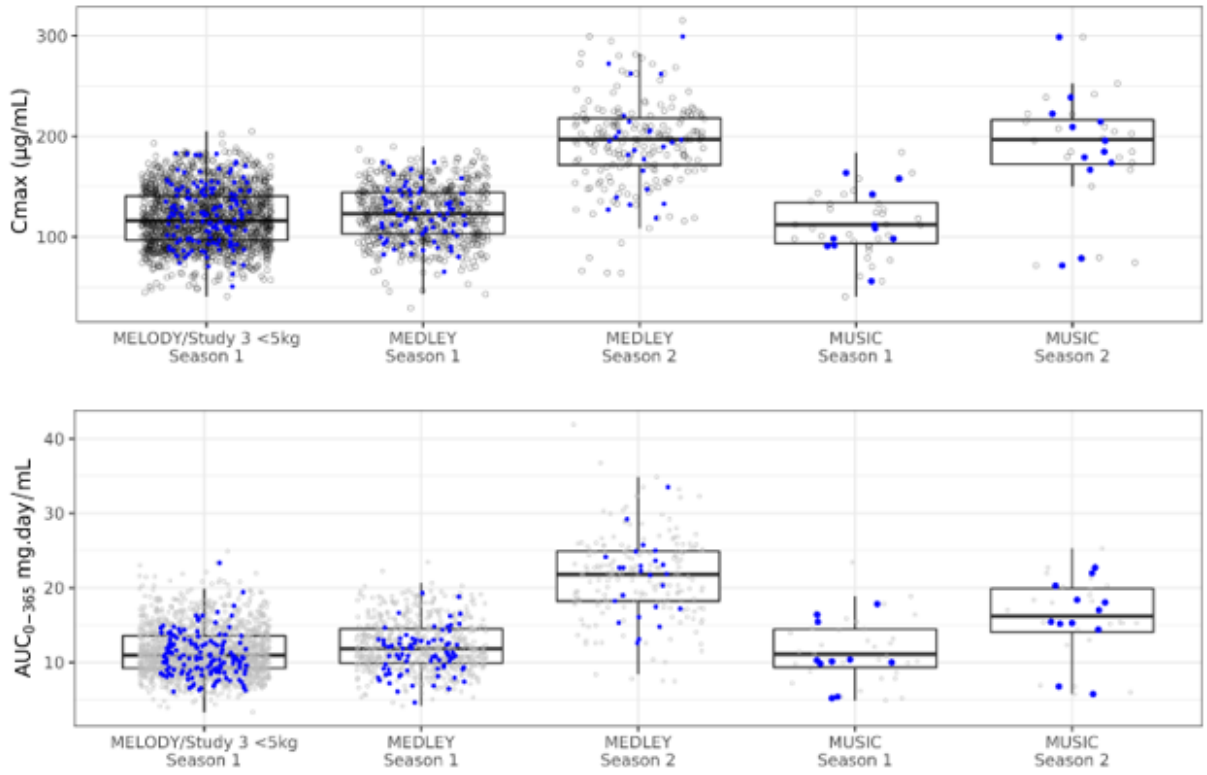


Box-and-whiskers and grey points represent all subjects. Red points represent subjects who had at least one AESI. Nirsevimab dose in Season 1: 50 mg < 5 kg, 100 mg ≥ 5 kg; Season 2: 200 mg.

AESI = adverse event of special interest; $AUC_{0\text{-}365}$ = predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; C_{max} = maximum plasma concentration; PK = pharmacokinetic(s).

Source: derived from the 2022 population PK report, Module 5.3.3.5, and the 2023 population PK report addendum, Module 5.3.3.5.

Figure Y Nirsevimab Exposure in MELODY, MEDLEY, and MUSIC Highlighting Subjects with at Least One SAE in Blue; C_{max} (Top), AUC_{0-365} (Bottom)



Box-and-whiskers and grey points represent all subjects. Blue points represent subjects who had at least one SAE. Nirsevimab dose in Season 1: 50 mg < 5 kg, 100 mg ≥ 5 kg; Season 2: 200 mg.

AUC_{0-365} = predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; C_{max} = maximum plasma concentration; PK = pharmacokinetic(s); SAE = serious adverse event.

Source: derived from 2022 population PK report, Module 5.3.3.5, and the 2023 population PK report addendum, Module 5.3.3.5.

In the MUSIC study (D5290C00008) nirsevimab was evaluated in immunocompromised (IC) children, below 2 years of age, in their first (46 children) and second RSV season (52 children + 2 children with wrong dose of 100 mg). In the first RSV season, either a 50 mg (weight < 5 kg) or 100 mg (weight >5 kg) IM dose of nirsevimab was administered on basis of bodyweight, whereas in the second RSV season an IM dose of 200 mg nirsevimab was administered, independent of bodyweight.

Secondary endpoint of the study was to evaluate PK and immunogenicity of nirsevimab. Additionally, efficacy was extrapolated on basis of the determined exposure and pre-specified exposure targets derived from the pivotal MELODY study in healthy children in their first RSV season.

The sparse PK-sampling scheme in the MUSIC study of 3 timepoints (Day 8 (few subjects), Day 31, Day 151 and Day361) for each subject was similar to the sampling scheme in the pivotal MELODY study. The main PK parameters, AUCbaselineCL and AUC0-365days, were calculated post-hoc from the popPK model. Furthermore, also the measured mean serum concentration of nirsevimab at day 151 was compared with data from the pivotal MELODY study. A time period of 151 days covers approximately the period of one RSV season.

In the MUSIC study it was demonstrated that the mean serum concentrations of nirsevimab at day 151 and mean-AUCbaselineCL in IC patients in their first (16.7 day*mg/mL, 25.6 µg/mL) and second (21 day*mg/mL, 33.2 µg/mL) RSV season were reasonable comparable to the mean serum concentration and AUCbaselineCL in the pivotal MELODY study (26.6 day*mg/mL, 21.3 µg/mL). The Applicant identified 14 PK-outliers in the MUSIC study with enhanced clearance. After a medical review, the Applicant claims that these 14 subjects have a medical condition associated with protein losing conditions in the 14 subjects, and provide this as an explanation for the enhanced clearance in these subjects.

Efficacy in the MUSIC study was extrapolated, according to the PIP, on the basis of the obtained PK data. The pre-defined criterion for extrapolation was derived from the MELODY study: > 80% of subjects achieving nirsevimab exposures ≥ the efficacy exposure target (AUCbaseline CL of 12.8 mg × day/mL). The efficacy target was not achieved in RSV season 1 (71.7%) and RSV season 2 (78%) and could only be achieved when the identified 14 PK-outlier were excluded in the analysis, RSV season 1 (80.5%) and RSV season 2 (92.7%).

The MAH provided an overview of exposure across MELODY, MEDLEY Season 1 and 2, and MUSIC Season 1 and 2 with occurrence of safety events SAE or AESI highlighted. The boxplots do not indicate any relation of exposure to subjects experiencing SAEs or AESIs.

In conclusion, it has been demonstrated by the MAH that exposure (AUCbaselineCL and day 151 serum conc.) in IC children of nirsevimab is reasonable comparable with healthy children in the Melody study. The PIP defined PK efficacy criteria could only be met if the 14 outliers were excluded in the analysis.

Pharmacokinetic interaction studies

NA

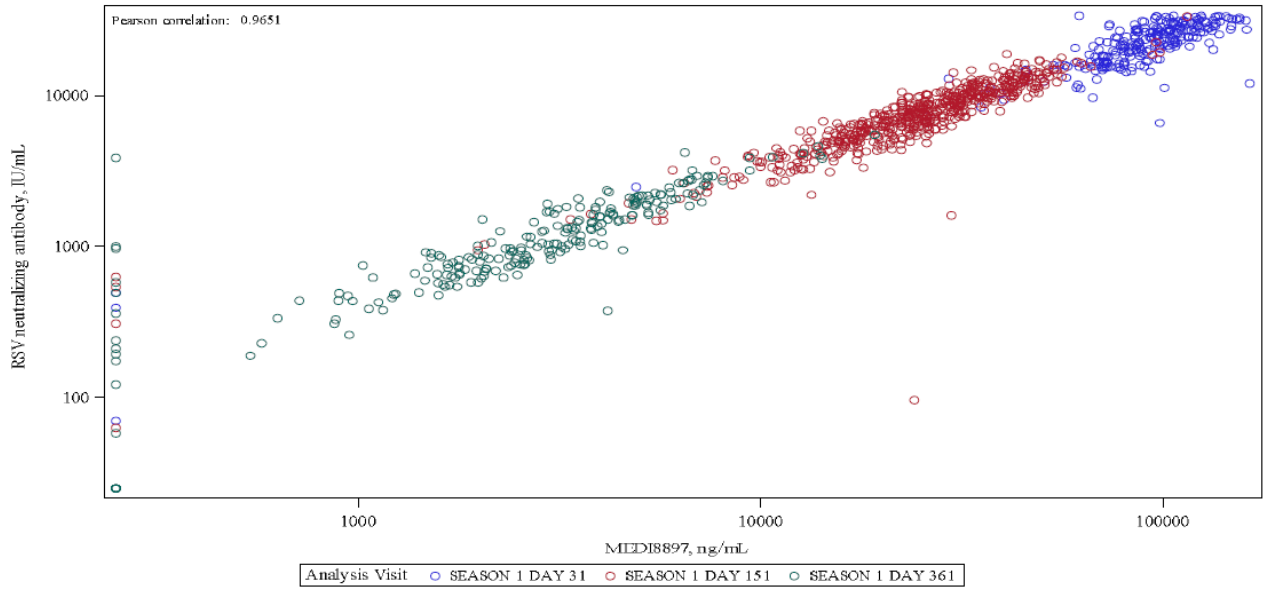
Pharmacokinetics using human biomaterials

NA

2.3.3. Pharmacodynamics

Following administration of a single dose of nirsevimab in infants entering their first RSV season in MEDLEY, dose-dependent increases in serum anti-RSV-neutralising antibody levels were seen, similar to the increases in nirsevimab serum concentrations. Serum anti-RSV-neutralising antibody levels were correlated with nirsevimab serum concentrations across all timepoints, confirming anti-RSV-neutralising activity of nirsevimab showing an almost linear exposure-response relationship.

Figure 21 **Correlation between Anti-RSV-Neutralising Antibody and Nirsevimab Serum Concentrations in Infants in the Nirsevimab Group - MEDLEY (Season 1) (As-treated Population)**



The Pearson correlation is calculated based on log-transformed RSV-neutralising antibody concentration and log-transformed nirsevimab concentration.

For serum concentration measurements of nirsevimab or RSV-neutralising antibody reported less than LLOQ, half of the LLOQ was assigned.

LLOQ = lower limit of quantitation; MEDI8897 = nirsevimab; RSV = respiratory syncytial virus.

Source: Figure 14.2.8.1.1, MEDLEY iCSR dated 31 August 2022, Module 5.3.5.1.

The RSV-neutralising antibody levels for infants who received nirsevimab waned between days 151 and 361 as expected but remained more than 5 times greater than baseline levels in subjects in MEDLEY Season 1, as seen in MELODY and Study 3.

A nearly linear exposure-response relationship for anti-RSV-neutralising activity of nirsevimab was shown in the first RSV season in Medley. There is no reason to suspect any differences in the exposure-response relationship for second seasons.

Immunogenicity

The existing ADA dataset was updated with data from Medley season 2 (data available through at least Day 151) and new ADA analyses from MUSIC (data available for all subjects through at least Day 151 of either RSV Season 1 or RSV Season 2).

For the CLD/CHD subjects in the NIRS/NIRS group with samples available for ADA assessment in Season 2, ADA was detected in 7/173 (4.0%) subjects at Season 1 Day 361. In Season 2, ADA was detected in 1/90 (1.1%) and 0/158 (0.0%) subjects at Day 31 and Day 151, respectively. No subjects had ADA detected in two consecutive seasons. Limited data were available for Day 361 (66 subjects). For Music 4/97 (4.1%) patients had treatment-emergent ADAs; all 4 were positive for YTE and negative for nAb.

There was no apparent impact of ADA on PK (based on limited ADA data) or safety in Season 2 in MEDLEY and Music.

The additional ADA data from MEDLEY Season 2 and MUSIC did not show any new immunogenicity findings compared to the existing immunogenicity data. For subjects in the NIRS/NIRS group in MEDLEY who received nirsevimab in both seasons, the first dose of nirsevimab did not appear to prime an anti-drug immune response after the second exposure to nirsevimab in Season 2 nor did a second dose boost immune responses in previously ADA-positive subjects from Season 1. However, the sensitivity of the assay was poor, and the results might therefore not be representative. This is reflected in the SmPC Section 5.1

Clinical Virology

The potential for mAb escape to nirsevimab was evaluated in vulnerable paediatric populations through NGS of all RSV infections in these studies.

Medley:

None of the major or minor variants in the nirsevimab binding site of RSV A or RSV B identified in Seasons 1 and 2 of MEDLEY affected recombinant RSV susceptibility to nirsevimab.

Music:

Three binding site mutations in RSV B (I206M, Q209R, S211N) were observed in subjects from the MUSIC study, none of which evaluated in context affected susceptibility to palivizumab or nirsevimab. No cases of RSV A were identified in MUSIC as of the DCO.

The binding site of RSV A was conserved at all positions. RSV B binding site substitutions I206M, Q209R, S211N became increasingly prevalent during the conduct of the studies, all 3 substitutions as well as their combination retained fully susceptible to nirsevimab. No amino acid substitution that was responsible for loss of nirsevimab neutralisation was identified.

2.3.4. PK/PD modelling

Refer to above section “Pharmacokinetics”.

2.3.5. Discussion on clinical pharmacology

In this type II variation the MAH has submitted data from the two clinical studies MEDLEY and MUSIC. In the MEDLEY study part assessed in this variation, nirsevimab was evaluated in 220 children (<24 months) with chronic lung disease (CLD) or congenital heart disease (CHD) in their second RSV season. MEDLEY was a double blinded phase II/III study containing a palivizumab control arm. Of the 220 children, 180 children were treated with nirsevimab in their first RSV season and 40 children with pavlizumab.

In the MUSIC clinical study, an open-label uncontrolled phase II study, nirsevimab was evaluated in immunocompromised (IC) children in their first (n=46) and second (n=52) RSV season, below 24 months. A weight-based dose of either 50 mg (infants < 5 kg) or 100 mg (infants > 5 kg) nirsevimab was administered in the first RSV season whereas a dose of 200 mg nirsevimab was administered in RSV season 2, independent of bodyweight. In the MUSIC study, 8 subjects in their

first RSV season and 6 subjects in their second RSV season, mainly Ukrainians, discontinued the study due to the war with Russia.

The efficacy of nirsevimab in the MEDLEY and MUSIC study population was assessed by PK extrapolation in accordance with the PIP. A similar sparse PK-sampling scheme with 3 time-points (15/31 days, 151 days, 361 days after dosing) was applied in all of the clinical studies. A time period of 151 days, corresponding to 5 months, covers approximately a RSV season which goes from autumn to spring.

The previously validated bioanalytical (nirsevimab PK) and immunogenicity methods (ADA, nAB and anti-YTE AB) were applied for the clinical studies reported in this variation. The screening ADA assay have poor drug tolerance and may result in false negative results for ADA samples collected before Day 361, which is also reflected in the immunogenicity results of MEDLEY and MUSIC. Almost no samples tested positive prior to Day 361 where the drug concentration was higher and the assay sensitivity greatly reduced. Test for ADAs against the YTE substitution was only performed on confirmed ADA positive samples. Thus, immunogenicity for nirsevimab 200 mg 2nd Season treatment is not considered adequately evaluated. This is reflected in the SmPC.

The final Pop PK model based on data from MELODY and MEDLEY, was used to predict data from the MUSIC study in immunocompromised children who received nirsevimab in Season 1 (n=46) and in Season 2 (n=50). The data from MUSIC was enclosed in the Pop PK dataset and fitted without re-estimation of parameters. Following the 2nd 200 mg Season 2 dose, 14 subjects had concentration profiles with notable higher clearances which could not be captured by the model. A “Clinical conditions” effect was added on clearance and parameters re-estimated. Clearance was estimated to increase by approximately 70% in subjects with one of four different protein losing conditions (nephrotic syndrome, GVHD, chronic liver disease, and Omenn syndrome).

The SmPC have been updated appropriately with the final PK-parameters derived from the updated popPK model. The same covariates were determined to be significant in the final pop-PK model as in previous pop-PK models, body weight remains the most important covariate.

In the MEDLEY study, RSV season 2, it was demonstrated that nirsevimab’s mean serum concentration in CHD and CLD patients at day 151 were comparable and that it was approximately 1.8 fold higher, than in the MEDLEY study, RSV season 1 and in the pivotal MELODY study. Post hoc. predicted exposure mean-AUCbaselineCl (29.5 day*mg/mL) was also approximately 1.4 fold higher. Mean baseline concentration was negligible, showing that the higher exposure in season 2 is not due to accumulation. The increased exposure in RSV season 2 could potentially influence the safety profile, though it was also shown by the MAH that the higher mean exposure was below what is considered as a safe exposure in healthy adults (59.5 day*mg/mL, 3000 mg IV dose). Additionally, previous treatment of nirsevimab in first RSV season appears not to impact (reduce) the exposure in RSV season 2. The efficacy of nirsevimab in CLD and CHD children in RSV season 2 was assessed by PK extrapolation according to the PIP. It was demonstrated that nirsevimab exposures were above the efficacious target level, AUCbaselineCL 12.8 mg·day/mL,in overall 98.4% of the children.

In the MUSIC study it was demonstrated that the mean serum concentrations of nirsevimab at day 151 in IC children in their first (25.6 µg/mL) and second RSV season (33.2 µg/mL) were comparable to the mean serum concentration in the pivotal MELODY study (26.6 µg/mL). The AUCbaselineCL in IC children in their first (16.7 mg·day/mL) and second RSV season (21 mg·day/mL) were also reasonable comparable to the mean serum concentration and AUCbaselineCL in the pivotal MELODY study (21.3 mg·day/mL). The Applicant identified 14 PK-outliers in the MUSIC study with enhanced clearance in RSV season 1 and 2. After a medical review

of the 14 outliers, the Applicant identified different clinical condition (Nephrotic syndrome, Omenn syndrome, malignancy, chronic liver disease, hiv) which on basis of literature (e.g. Otani et al. 2022) was associated with protein losing conditions (nephrotic syndrome or protein-losing enteropathy). This condition was suggested as an explanation for the enhanced clearance. Upon request, the Applicant has shown that 31 subjects in the MUSIC study having one of the identified clinical conditions did not have high clearance. Furthermore, it was not possible to provide further support for the proposed hypothesis with relevant biomarkers such as serum albumin or IgG, as no samples was left, and it was also argued that the levels of these biomarkers are difficult to interpret. Overall, the hypothesis proposed by the MAH to account for the outliers is acknowledged, though it is also clear that a medical condition is not enough to classify the nirsevimab clearance of subjects. It was concluded by the Applicant that it is not possible to identify patients with high clearance prior to treatment. This conclusion is justified from the arguments and analysis discussed above. A warning regarding high clearance in some IC patients has been included in the SmPC, section 4.4.

Efficacy in MUSIC study was extrapolated, according to the PIP, on basis of the obtained PK data. The efficacy target was not achieved in RSV season 1 (71.7%) and RSV season 2 (78%) and could only be achieved when the identified 14 PK-outliers with high clearance were excluded in the analysis: RSV season 1 (80.5%) and RSV season 2 (92.7%). The Applicant has argued that though the protection for RSV virus do not match the level of full 5 months protection observed in the pivotal MELODY study, in healthy infants, the immunocompromised children with high clearance receive benefit of the treatment. This argument is supported. The Applicant has suggested to include a statement in section 4.4 of the SmPC regarding the associated risk of high clearance of nirsevimab. A rapid decline in nirsevimab serum concentration was observed in 14% (14/96) of the immunocompromised patients from the MUSIC study. It has not been possible to identify risk factors that would allow identification of these patients. It should be noted that in these patients, the mean nirsevimab serum concentrations and the mean exposure were reasonable comparable to the mean exposure seen in the pivotal MELODY study. A warning is added in SmPC section 4.4, and the issue to be followed in the PSUR: "*The MAH should monitor lack of efficacy data and potential risk factors in patients with protein-losing conditions leading to high clearance of nirsevimab and to submit a literature review on this issue in the next PSUR".* In response to the above request from CHMP, the MAH has agreed to submit a literature review in the next PSUR concerning patients with protein-losing conditions.

It was furthermore shown that the predicted highest expected exposure (AUC0-365days) of nirsevimab in RSV season 2 in children with lowest body weight (6.5 kg) was below the predicted safe exposure in adults. For reference then the mean body weight of subjects in the MEDLEY study in RSV season 2 was 9.88 kg and the minimum weight was 6.1 kg and maximum weight was 15.7 kg. In MEDLEY RSV Season 2, a total of 6 subjects weighed < 7 kg on Day 1 of RSV Season 2, of which 5 received the projected Season 2 treatment. Treatment emergent AEs were reported for all 5 subjects. All 5 subjects experienced higher than average exposure which ranged from 154.07 µg/mL to 251.30 µg/mL at Day 31 and from 1.8 µg/mL to 84.08 µg/mL at Day 151. Safety data was collected for subjects who received Season 2 treatment from MEDLEY and MUSIC. Boxplots of exposure-safety data from MELODY Season 1 and MEDLEY and MUSIC Season 1 and 2 did not indicate any relation of subjects with AEs of Grade 3 or higher severity or SAEs, and subjects with AESIs to Cmax or AUC0-365.

Exposure simulations based on extreme high body weight, defined as infants in Season 2 weighing ≥ 13 kg at the time of dosing, indicated that the Day 151 serum concentration would be within the

exposure range of MELODY Season 1 and the Dose 2 AUC0-365 most likely be above the target AUC of 12.8 day·mg/mL previous identified as the efficacy threshold for optimal protection.

Evaluation for potential mAb escape through NGS of all RSV infections showed the binding site of RSV A was conserved at all positions. RSV B binding site substitutions I206M, Q209R, S211N became increasingly prevalent during the conduct of the studies, all 3 substitutions as well as their combination retained fully susceptible to nirsevimab. No amino acid substitution that was responsible for loss of nirsevimab neutralisation was identified.

2.3.6. Conclusions on clinical pharmacology

The provided pharmacokinetic data supports the use of nirsevimab to prevent RSV infection in children with CLD, CHD and IC children in their first and second RSV season.

The potential impact of increased clearance of nirsevimab in immunocompromised subjects with protein-losing conditions in terms of efficacy will be further investigated, ie. the *MAH will monitor lack of efficacy data and potential risk factors in patients with protein-losing conditions leading to high clearance of nirsevimab and submit a literature review on this issue in the next PSUR".*

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

A 200 mg dose is proposed for the chronic lung disease (CLD) and congenital heart disease (CHD) patients entering their second RSV season. 50 and 100 mg were used for the first RSV season. No dedicated dose-response study was conducted with the 200 mg dose that is proposed for the second RSV season.

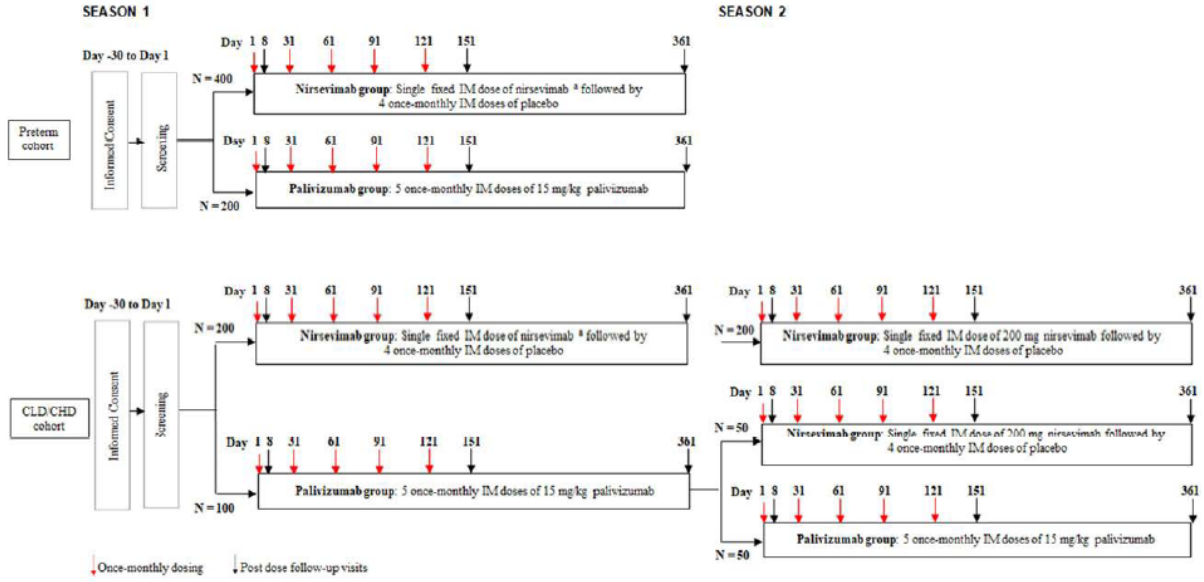
Taking into account the anticipated increase in body weight at the time for second RSV season treatment (8.5 to 15 kg), modelling suggests that the target exposure of AUC 12.8 day·mg/mL is achieved and maintained with a dose of 200 mg. As mentioned in the pharmacology section, the 200 mg dose results in exposures almost twice the approved 50 and 100 mg Season 1 doses. Please refer to the pharmacology section.

2.4.2. Main study

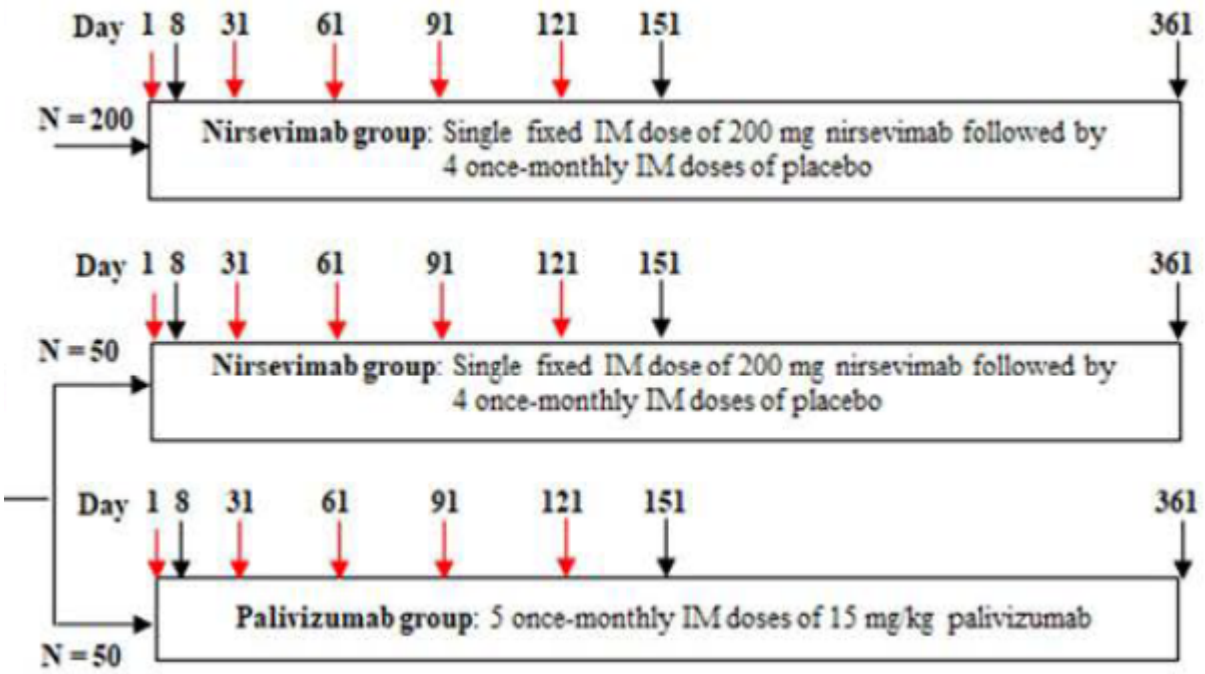
MEDLEY: A Study to Evaluate the Safety of MEDI8897 for the Prevention of Medically Attended Respiratory Syncytial Virus (RSV) Lower Respiratory Track Infection (LRTI) in High-risk Children.

MEDLEY is an ongoing pivotal Phase II/III randomised, double-blind, palivizumab controlled study to evaluate the safety, PK, ADA response, and descriptive efficacy of nirsevimab in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2, respectively).

Figure 22 **Flow Chart of Study Design**



SEASON 2:



[a] In the nirsevimab group Season 1, dose level was stratified by body weight at time of dosing; subjects received 50 mg nirsevimab if weighing < 5 kg or 100 mg nirsevimab if weighing ≥ 5 kg.

SEASON 1: Randomisation for Season 1 Day 1, 2:1 nirsevimab or palivizumab.
SEASON 2 (CLD/CHD cohort only): Randomisation for Season 2 Day 1: Subjects who were randomised in Season 1 to receive nirsevimab will receive nirsevimab in Season 2. Subjects who were randomised to receive palivizumab in Season 1 received nirsevimab or palivizumab in Season 2.
Blood samples for PK and ADA: Season 1 for both cohorts – Screening or Day 1 predose and on Days 31 (predose), 151, and 361 (for CLD/CHD cohort, prior to Season 2 dosing); Season 2 for CLD/CHD cohort only - Days 31 (predose), 151, and 361. Additionally, samples are being collected during both seasons from all subjects hospitalised for a respiratory infection, and before and after surgery with cardiopulmonary bypass for subjects with CHD requiring a replacement dose of investigational product.
Safety assessments will be performed through 360 days post first dose for each respective season.
ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular; PK = pharmacokinetic.

Methods

Study participants

Participating patients were the CLD/CHD cohort from the MEDLEY Season 1 study, i.e. patients who had received either nirsevimab or palivizumab.

Subjects included for the second season part of the MEDLEY study were those with chronic lung disease (CLD) and congenital heart disease (CHD) from the initial CLD/CHD cohort of MEDLEY (first season). Children from the preterm cohort from the MEDLEY study were not included for the second season intervention.

The revised indication reflects the study population included in MEDLEY for the second season:

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

1 Neonates and infants during their first RSV season.

2 Children up to 24 months of age who remain vulnerable to severe RSV disease during their second RSV season (see section 5.1)

Beyfortus should be used in accordance with official recommendations.

Subjects included for the second season part of the study had all received either nirsevimab (n=200) or palivizumab (n=100) during their first RSV season, hence, not all patients had received nirsevimab previously. This is adequately reflected in the SmPC section 5.1.

Treatments

Subjects who had received nirsevimab before or during the first RSV season were assigned to nirsevimab 200 mg IM followed by 4 once-monthly IM doses of placebo (n=200) and subjects who had received palivizumab before or during the first season were randomly assigned to either Nirsevimab 200 mg IM followed by 4 once-monthly IM doses of placebo or Palivizumab 15 mg/kg IM once-monthly for 5 months in a 1:1 fashion.

Objectives

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

Outcomes/endpoints

The primary endpoint in the MEDLEY trial was safety. Efficacy endpoints were part of the secondary endpoint or explorative endpoints.

Efficacy is based on extrapolation which was agreed by the PDCO.

Secondary endpoint:

- Incidence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2
- Incidence of hospitalisations due to RT-PCR-confirmed RSV through 150 days after Dose 1 for Season 1 and Season 2

Exploratory endpoints:

- Anti-RSV neutralizing antibody levels (IU/mL) in serum for nirsevimab recipients compared to palivizumab recipients
- Summary of serum RSV neutralising antibody levels (may include GMT, GMFR, C_{max}, apparent clearance, and $t_{1/2}$)
- Antibody levels to RSV F, Ga, Gb, or N at different time points
- Changes in RSV antibody levels (seroresponse) indicating exposure to RSV
- RSV antigen antibody levels (AbU/mL) to multiple RSV antigens
- Summary of serum RSV antibody levels (may include GMT, GMFR, seroconversion rates, apparent clearance, and $t_{1/2}$)
- Magnitude of HRU (eg, number of admissions to hospitals and ICUs and duration of stay; number of subjects who required respiratory support and supplemental oxygen and the duration of use; number and type of outpatient visits [eg, ER, urgent care, outpatient clinic]; and number of prescription and OTC medications use) for nirsevimab recipients compared to palivizumab recipients
- Caregiver burden (eg, caregiver missed workdays, subject absence from day care) for subjects with MA LRTI caused by RT-PCR-confirmed RSV Incidence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV from Day 152 to Day 361 for Season 1 and Season 2

Criteria for the MA LRTI is the same as in MELODY and Study 3 (evaluated at time of initial MAA), with an addition of prescription of new or increased dose of medications (bronchodilators, steroids, diuretics, cardiac medication) because the CLD/CHD cohort were using this background treatment.

Sample size

No sample size calculation was presented for the second season study. All subjects from the CLD/CHD cohort were invited as described below.

Approximately 900 palivizumab eligible infants entering their first RSV season were to be enrolled into 1 of 2 cohorts (Figure 1 above): (1) preterm cohort, including approximately 600 preterm infants (≤ 35 wGA) without CLD/CHD, or (2) CLD/CHD cohort, including approximately 300 infants with CLD of prematurity or haemodynamically significant CHD. A minimum of 100 infants with haemodynamically significant CHD were to be enrolled.

Randomisation

The randomization was stratified by age group and hemisphere in MEDLEY first season. The randomization was not stratified by CLD/CHD disease. The two cohorts (preterm and CLD/CHD) were balanced between treatment groups. The study was double-blinded.

Subjects who were randomised to nirsevimab for Season 1 were to receive a single fixed IM dose of 200 mg nirsevimab followed by 4 once-monthly IM doses of placebo.

Subjects who were randomised to palivizumab for Season 1 were to be re-randomised 1:1 to either nirsevimab or palivizumab. See treatment above.

Blinding (masking)

The study was double blinded. However, after the data base lock for the primary analysis and before the data base lock for the second season analysis, season 1 data were unblinded to the Sponsor and designated clinical research organisation personnel associated with the primary analysis, write-up, and submission only; therefore, individual treatment assignments in Season 1 were known to these personnel.

The MAH has clarified that to ensure unbiased data review and cleaning, subject management and safety monitoring, the MAH and CRO personnel remained blinded to subject-level data of MEDLEY until the end of study.

Furthermore, the MAH has stated that regardless of season, site personnel, participants, and the study team members who participated in the advice or decisions involving study subjects and/or day-to-day interactions with the site, remained blinded until the end of the study to ensure the study integrity was maintained.

Statistical methods

Three analyses were planned for this study: the Primary Analysis, Season 2 Analysis and the final analysis (Table 18).

The Primary Analysis was presented with the initial application and in a subsequent variation.

The statistical analysis of the efficacy data in season 2 is purely descriptive. Furthermore, extrapolation was used to assess efficacy. Please refer to the pharmacology section.

Season 2 Analysis was conducted after all the CLD/CHD cohort subjects had completed follow-up through the second 5-month RSV season (ie, through at least 150 days post first dose in Season 2).

Table 19 **Summary of Key Analyses in MEDLEY**

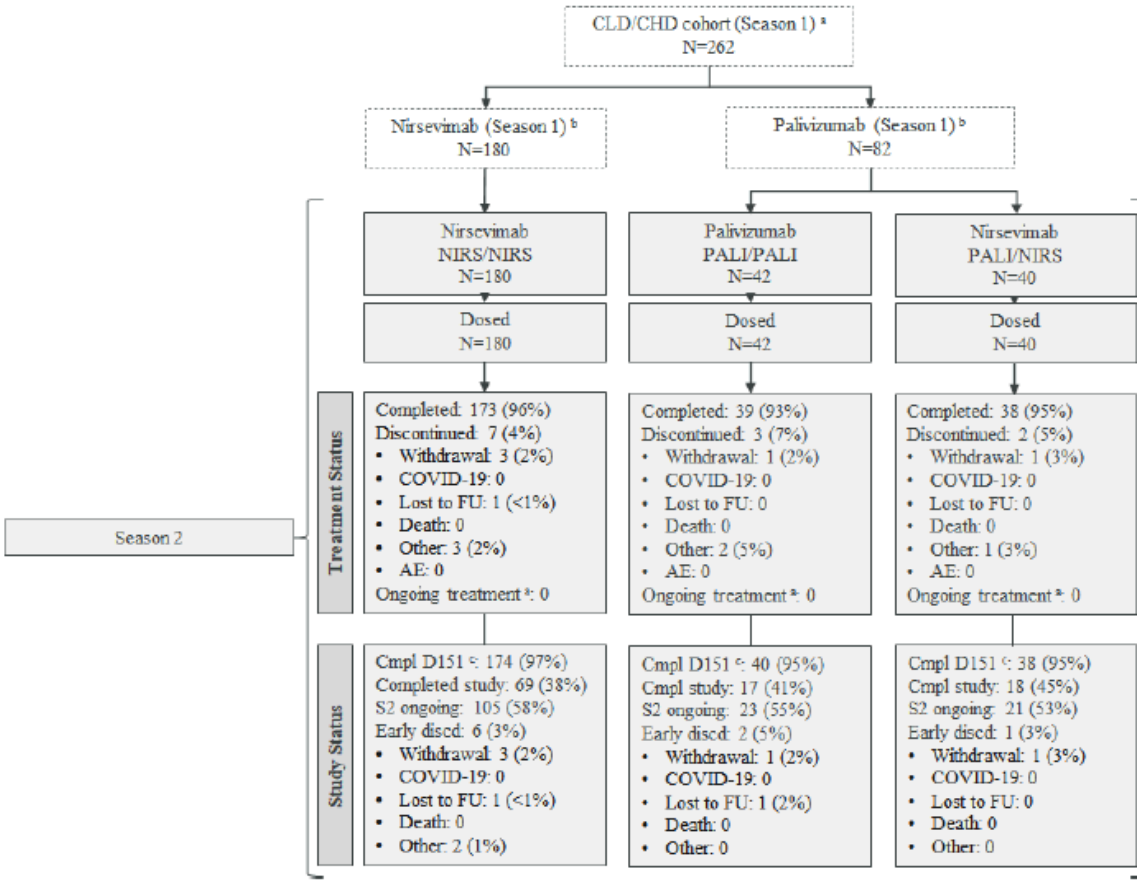
Analysis	Trigger for analysis	DCO (DBL)	Data included in analysis	Analysis population (N)	Follow-up	Location of data report
Primary	All randomised subjects completed follow-up through the first 5-month RSV season (Season 1 Day 151)	03 May 2021 (10 June 2021)	All Season 1 safety, efficacy, PK, and ADA data available at the time of the data cut-off.	Season 1: Overall population (925), comprising the preterm (615) and CLD/CHD (310) cohorts	At least 150 days post first Season 1 dose.	Superseded by current iCSR
Season 2	All CLD/CHD subjects [a] completed follow-up through the second 5-month RSV season (Season 2 Day 151).	30 April 2022 (31 May 2022) [b]	All Season 1 and Season 2 safety, efficacy, PK, and ADA data available at the time of the data cut-off.	Season 1: Overall population (925), comprising the preterm (615) and CLD/CHD (310) cohorts	360 days post first Season 1 dose.	iCSR (summary outputs in Section 14)
				Season 2: CLD/CHD cohort (262)	At least 150 days post first Season 2 dose.	
Final	All CLD/CHD subjects [a] completed the last visit of the study (Season 2 Day 361).	TBD	All Season 1 and Season 2 data collected in the study.	Season 1: Overall population (925), comprising the preterm (615) and CLD/CHD (310) cohorts Season 2: CLD/CHD cohort (262)	360 days post first Season 1 dose. 360 post first Season 2 dose.	Subsequent final CSR

[a] All subjects from the CLD/CHD cohort who were randomised to receive a second course of study treatment in the Season 2 phase of the study.
[b] Date last Season 2 analysis output was created: 18 August 2022.
Note that previously reported analyses may change in subsequent CSRs where additional data become available a=post-database lock.
ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; CSR = clinical study report; DBL = database lock (date); DCO = data cut-off (date); iCSR = interim CSR (ie, the current report); N = number of randomised subjects in analysis; PK = pharmacokinetic; RSV = respiratory syncytial virus; TBD = to be determined.

Results

Participant flow

Figure 23 **Subject Disposition (Season 2)**



[a] Subjects from the Season 1 CLD/CHD cohort who were re-randomised in Season 2.
[b] Subjects from the Season 1 CLD/CHD cohort were re-randomised to nirsevimab or palivizumab.
[c] Numerator includes subjects whose study status was ongoing on Season 2 Day 151.
AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; Cmpl = completed; COVID-19 = coronavirus disease 2019; D151 = Day 151; Discd = discontinued; FU = follow-up; NIRS = nirsevimab; PALI = palivizumab; S2 = Season 2.
Source: Table 14.1.1.2 and Listing 16.2.1.4.

Recruitment

In the overall population (CLD/CHD cohort and preterm cohort), 960 subjects were screened, of whom 925 were enrolled and randomised (2:1) to nirsevimab (n = 616) or palivizumab (n = 309).

In the CLD/CHD cohort, 310 subjects were randomised to nirsevimab (n = 209) or palivizumab (n = 101). Of these subjects, 306 were dosed. A total of 299 subjects (96.5%), including 204 (97.6%) in the nirsevimab group and 95 (94.1%) in the palivizumab group, had completed follow-up through 150 days post first dose.

262 subjects (84.5%), including 180 (86.1%) in the nirsevimab group and 82 (81.2%) in the palivizumab group, completed Season 1 and continued into season 2 of the study.

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

In season 2, subjects were enrolled at 58 study sites in 18 countries.

Conduct of the study

In total 262 subjects were randomised and dosed. Efficacy follow-up through at least 150 days post first dose in Season 2 was completed by 252 (96%), and 104 (40%) subjects completed follow-up through 360 days post dose in Season 2 (completed Season 2) at the time of the data cut-off for the Season 2 Analysis.

More subjects in the NIRS/NIRS treatment group had important protocol deviations (n=13, 7.2%), most pertaining to treatment compliance (9 subjects (5%)) and LRTI sample deviations (5 subjects (2.8%)). No subjects in the PALI/PALI and only 1 subject (2.5%) in the PALI/NIRS had important protocol deviations.

The MAH has clarified the differences in protocol deviations, and those are not considere related to the treatment allocation and therefore the imbalances in protocol deviations are considered due to chance variation.

Baseline data

A total of 225 (85.9%) subjects were White and 151 (57.6%) were male.

Baseline data consists of data from day 1 when children was treated in season 1. At time of dosing in season 2, median body weight was 9.7 kg with IQR of 8.9 kg to 10.9 kg (minimum body weight: 6.1 kg and maximum bodyweight of 15.7 kg) The body weight interval is discussed in the pharmacology section.

The proportion of CHD and CLD subjects were overall equally distributed across treatment groups. Across treatment groups, 72.1% of enrolled subjects in season 2 had CLD, 30.9% had CHD, 3.4% had Down syndrome and no subjects had cystic fibrosis.

Numbers analysed

All 262 subjects (180, 40, and 42, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively) were included in the ITT and As-treated Populations (Season 2).

Outcomes and estimation

There were no events of MA RSV LRTI or MA RSV LRTI hospitalisation during the 150 days post 1st injection in season 2. The study population has almost completed the full follow-up period, and from day 151 to day 360 only 1 event has occurred.

A number of secondary and exploratory endpoints were also evaluated; however, the results do not impact the efficacy evaluation (either low event numbers or less relevant for the indication). These will not be described further, as the efficacy is based primarily on PK extrapolation. (Table 19).

Table 20

Incidence of MA RSV LRTI by RSV Subtype and Reporting Period Through at Least 150 Days Post First Dose in Season 2 – ITT Population

Reporting period RSV subtype	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Through 150 days post first dose	0	0	0
RSV A	0	0	0
RSV B	0	0	0
From 151 to 360 days post first dose [a]	0/40 (0.0)	1/38 (2.6)	0/174 (0.0)
RSV A	0/40 (0.0)	1/38 (2.6)	0/174 (0.0)
RSV B	0/40 (0.0)	0/38 (0.0)	0/174 (0.0)
Through 360 days post first dose	0	1 (2.5)	0
RSV A	0	1 (2.5)	0
RSV B	0	0	0

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

ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; NIRS = nirsevimab; PALI = palivizumab; RSV = respiratory syncytial virus.

Source: Table 14.2.1.1.2 and Table 14.2.1.5.2.

Extrapolation

Please also refer to the clinical pharmacology section regarding extrapolation and modelling.

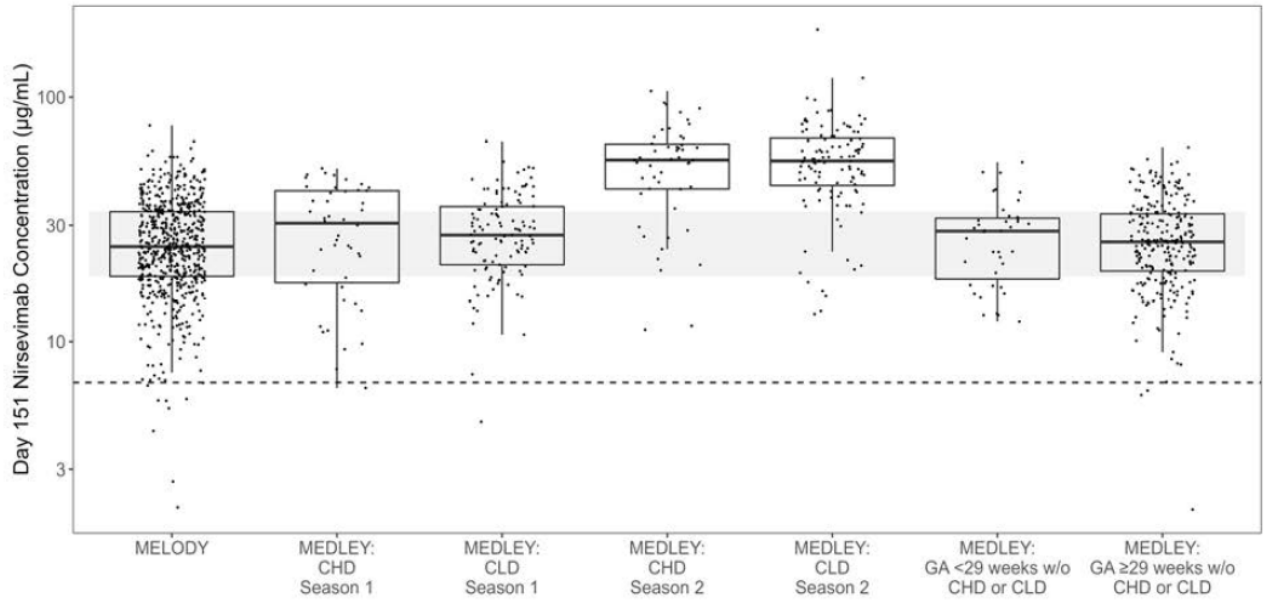
PK extrapolation for efficacy from MELODY (healthy infants) to MEDLEY (preterm, CLD and CHD patients) was accepted during the initial MAA for treatment during the first RSV season.

In the present submission, PK and clinical data from a second season treatment in MEDLEY has been submitted using a larger dose (200 mg vs 50/100 mg in the first season). In addition, PK and safety data from immunocompromised patients from the single-arm MUSIC study have also been submitted. It is agreed and in accordance with the PIP that an extrapolation approach of efficacy is acceptable.

Efficacy was considered to be demonstrated if the proposed doses resulted in serum nirsevimab exposures at or above the predicted efficacious target, based on exposure-response analysis, in > 80% of the MEDLEY population. In the MEDLEY population in Season 2, nirsevimab exposures were above the efficacious target (ie, AUCbaselineCL 12.8 mg·day/mL) in 98.4% (187/190) of the children, with no difference between the CLD and CHD cohort.

This is also shown in the figures below, where the observed nirsevimab serum concentrations (Figures 24 and 25 below) and the predicted exposure (Figures 26 and 27 below) in the second season is higher than seen in MELODY and MEDLEY season 1, which is reassuring from an efficacy point of view.

Figure 24 **Boxplots of Observed Day 151 Serum Concentrations in MEDLEY Subjects Compared to MELODY**

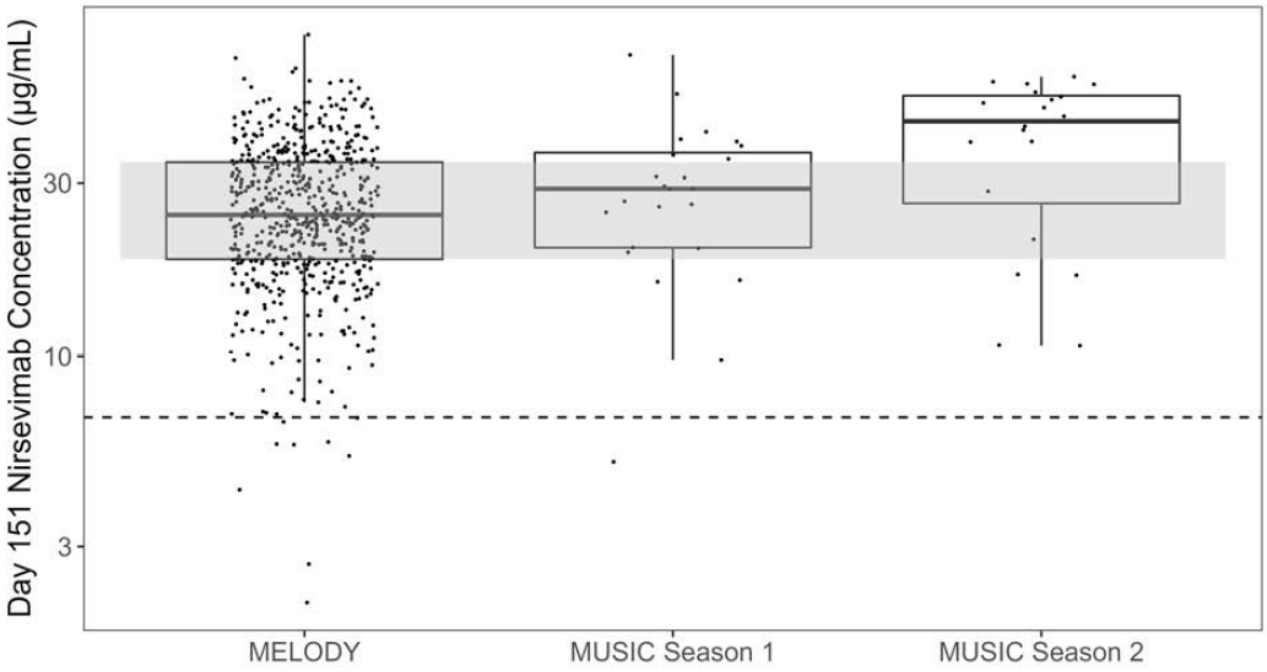


Day 151 concentrations are Visit Day 151 ± 14 days. Grey band is the reference inter-quartile range for MELODY Day 151. The horizontal dashed black line is the nonclinical EC90 (6.8 µg/mL). Data presented are paediatric subjects who are < 5 kg receiving 50 mg, ≥ 5 kg receiving 100 mg in Season 1, and/or receiving 200 mg in Season 2. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's syndrome) and was excluded for extrapolation. The 2 groups on the right, MEDLEY: GA < 29 weeks without CHD or CLD and MEDLEY: GA ≥ 29 weeks without CHD or CLD, contain only Season 1 subjects.

CHD = congenital heart disease; CLD = chronic lung disease; EC90 = 90% effective concentration; GA = gestational age.

Source: Figure 28, 2022 Population PK report. Module 5.3.3.5, this Variation.

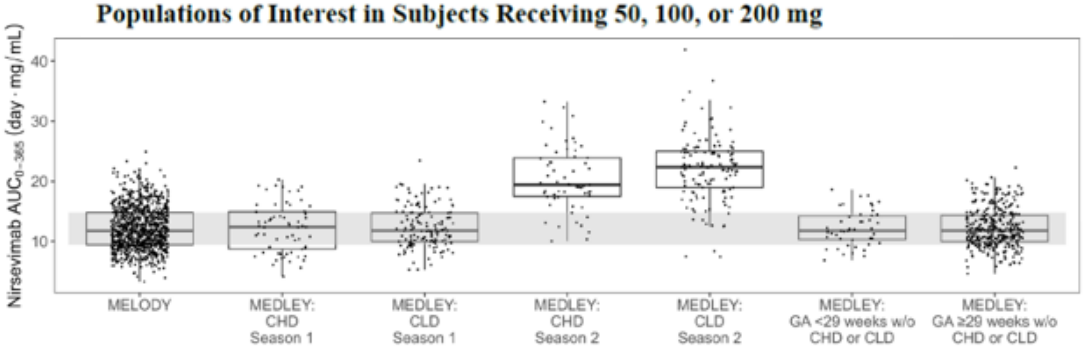
Figure 25 **Boxplots of Observed Day 151 Serum Concentrations in MUSIC Subjects Compared to MELODY**



Day 151 concentrations are Visit Day 151 ± 14 days. Grey band is the reference inter-quartile range for MELODY Day 151 concentrations. The horizontal dashed black line is the nonclinical EC90 (6.8 µg/mL). Subject 4305001 (MUSIC) was dosed 100 mg at age 12.2 months (flagged as Season 2) but was included in Season 1 for extrapolation. Data presented are paediatric subjects who are < 5 kg receiving 50 mg or ≥ 5kg receiving 100 mg in Season 1 or receiving 200 mg in Season 2.

EC90 = 90% effective concentration.

Figure 26 **Boxplots of Predicted AUC_{0-365} in MELODY and MEDLEY Grouped by Populations of Interest in Subjects Receiving 50, 100, or 200 mg**

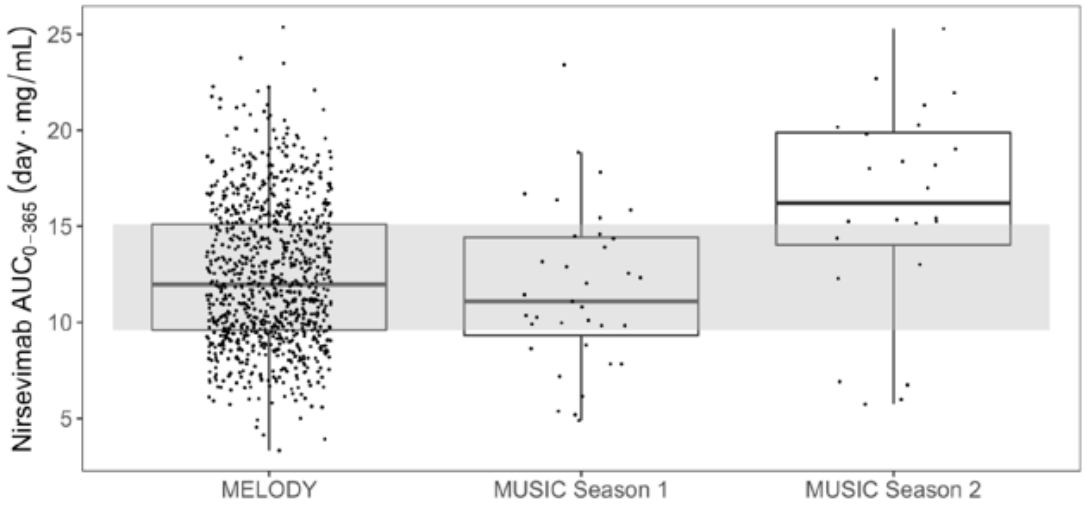


Source: ASTR-NIRSE-run-plots-bla-Aug2022.R

Notes: Grey band is the reference inter-quartile range for MELODY AUC_{0-365}. Data presented are pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg. One MEDLEY Season 2 subject (20047730001) was not CHD or CLD (Down's syndrome) and was excluded for extrapolation. The 2 groups on the right, MEDLEY: GA <29 weeks w/o CHD or CLD and MEDLEY: GA ≥29 weeks w/o CHD or CLD, contain only Season 1 subjects.

Abbreviations: AUC_{0-365}=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model; CHD=congenital heart disease; CLD=chronic lung disease; GA=gestational age; w/o=without

Figure 27 **Boxplots of Predicted AUC_{0-365} in MELODY and MUSIC Grouped by Season**



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R
Notes: Grey band is the reference inter-quartile range for MELODY AUC_{0-365}. Subject 4305001 (MUSIC) was dosed 100mg at age 12.2 months (flagged as Season 2) but was included in Season 1 for extrapolation. Data presented are pediatric subjects who are <5kg receiving 50mg, ≥5kg receiving 100mg, or receiving 200mg.
Abbreviations: AUC_{0-365}=predicted area under the serum concentration-time curve from Days 0 to 365 derived using densely predicted concentration-time curves from the final model

Ancillary analyses

Not applicable

Summary of main study

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

Table 21 *Summary of Efficacy for trial MEDLEY season 2*

Title: A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (		
Study identifier	MEDLEY	
Design	A global randomised, double-blind palivizumab controlled trial	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	360 days + 150 days
Hypothesis	No hypothesis testing. Descriptive data only Data from the second RSV season is analysed, which is 150 days post first dose in season 2.	
Treatments groups	Palivizumab/Palivizumab	Palivizumab 15 mg/kg I.M. monthly injection x 5 during the first RSV season Palivizumab 15 mg/kg I.M. monthly injection x 5 during the second RSV season N=42

	Palivizumab/Nirsevimab		Palivizumab 15 mg/kg I.M. monthly injection x 5 during the first RSV season Nirsevimab 200 mg x 1 during second season + 4 x placebo N=40	
	Nirsevimab/Nirsevimab		Nirsevimab x 1 during first season (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ⩾ 5 kg) + 4 x placebo Nirsevimab 200 mg x 1 during second season + 4 x placebo N=180	
Endpoints and definitions				
	Secondary	MA RSV LRTI	Medically attended lower respiratory tract infection	
	Secondary	MA RSV LRTI with hospitalisation	Medically attended lower respiratory tract infection with hospitalisation	
Database lock	31 May 2022			
Results and Analysis				
Analysis description	Secondary Analysis			
Analysis population and time point description	Intent to treat and Per protocol (numbers are the same) Day 150 post dose in RSV season 2			
Descriptive statistics and estimate variability	Treatment group	Palivizumab/Palivizumab	Palivizumab/Nirsevimab	Nirsevimab/Nirsevimab
	Number of subject	42	40	180
	MA RSV LRTI (n (%))	0	0	0
	MA RSV LRTI with hospitalisation (n (%))	0	0	0
Notes	Data from first season was presented and evaluated with the initial marketing authorisation application.			

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

NA

Clinical studies in special populations

NA

Supportive study

MUSIC: A phase 2, open-label, uncontrolled, single-dose study to evaluate the safety and tolerability, pharmacokinetics, and occurrence of antidrug antibody for nirsevimab in immunocompromised children ≤ 24 months of age.

The methodology and extrapolation of efficacy in immunocompromised patients are discussed in details in the pharmacology section.

Objectives:

Primary objective: To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age.

Secondary objectives: To evaluate the PK of nirsevimab, ADA responses to nirsevimab in serum, and descriptive efficacy of nirsevimab when administered as a single IM dose to infants ≤ 24 months of age.

Efficacy endpoints

Efficacy endpoints (secondary): Incidence of medically attended LRTI (inpatient and outpatient) and hospitalisations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab.

Serum concentrations of nirsevimab and ADA

Serum concentrations of nirsevimab at selected time points were evaluated as a secondary endpoint to confirm that serum concentrations were maintained at an efficacious level for at least 5 months after dosing. To determine nirsevimab serum levels post dosing and to correlate with the potential development of ADA, serum concentrations were measured up to 360 days post dose.

ADA to nirsevimab were measured at selected time points throughout the study and up to 360 days post dose.

Study population

The study enrolled subjects in Japan, South Africa, the USA, and the EU.

Inclusion criteria:

- Neonate, infant, or young child ≤ 24 months of age who, per Investigator judgement, were:

  (a) In their first year of life and entering their first RSV season at the time of dose administration.

  OR

(b) In their second year of life and entering their second RSV season at the time of dose administration.

- Subjects were required to meet at least one of the following conditions: immunodeficiency (combined, antibody, or other aetiology); HIV infection; organ or bone-marrow transplantation; receiving immunosuppressive chemotherapy, systemic, high-dose corticosteroid therapy, or other immunosuppressive therapy.

Exclusion criterion: Subjects who had previously received palivizumab were excluded.

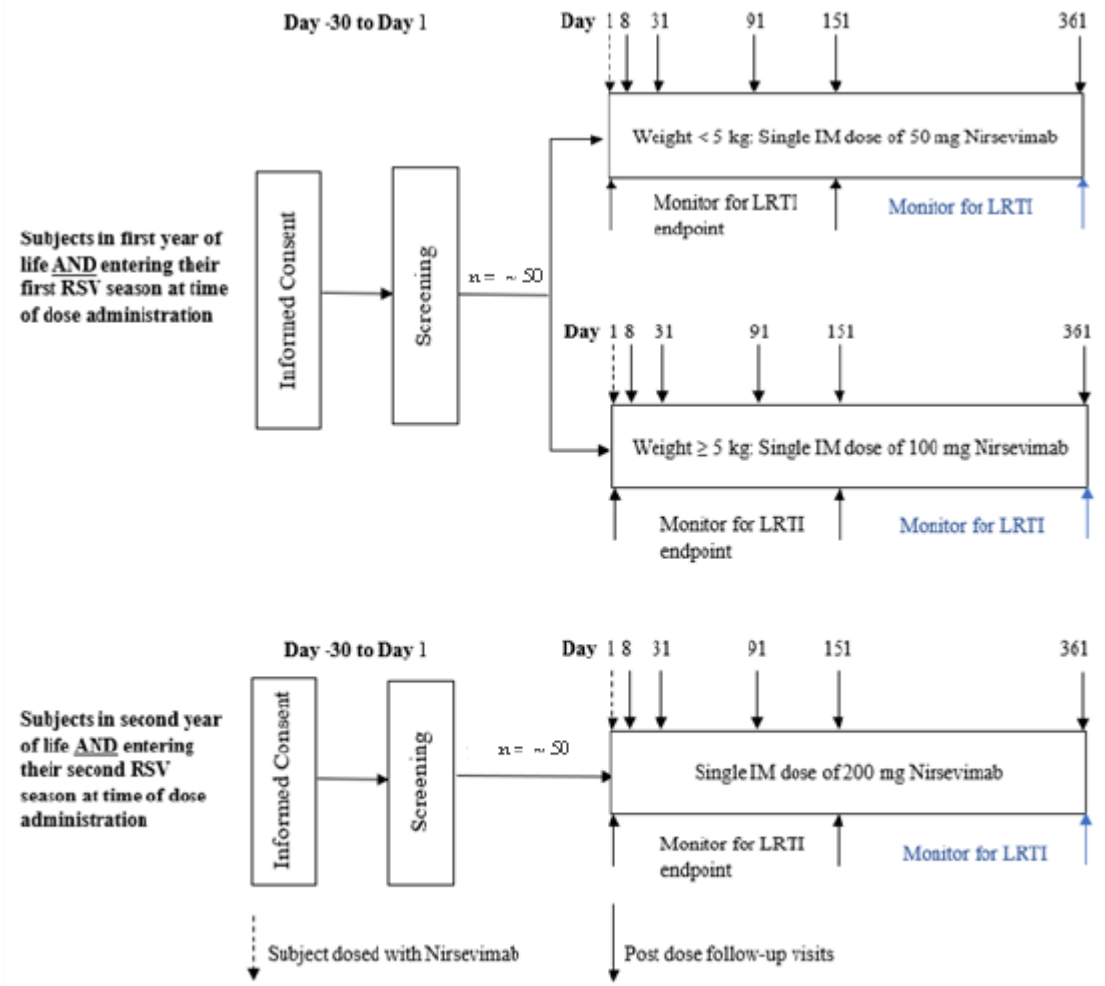
Treatment:

Approximately 50 subjects entering their first RSV season were planned to receive nirsevimab as a single, fixed IM dose of 50 mg if body weight < 5 kg or 100 mg if body weight ≥ 5 kg. Approximately 50 subjects entering their second RSV season were planned to receive nirsevimab as a single, fixed IM dose of 200 mg.

Trial design

See figure 28:

Figure 28 **Flow Chart of Study Design**



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

Analysis plan: Subjects were to be followed approximately 1 year after dose administration. Subjects were monitored throughout the study for LRTI. A planned interim analysis was conducted when subjects enrolled globally by end of 2021 were followed through Day 151 post dosing (N = 60). A second planned analysis was conducted when all subjects had been followed up through at least 150 days post dose (N = 100). All available safety, PK, ADA, and descriptive efficacy data collected for these subjects were included in the interim analyses.

Results:

Disposition: 106 children were screened, and 100 children were included of which 48 children were dosed in their first RSV season and 52 children were dosed in their second RSV season. The children were followed for medically attended LRTI (inpatient and outpatient) and hospitalisations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab and additionally followed for safety until day 361.

Out of the 100 enroled children, 94 completed the 361 days follow-up. Hence, 6 subjects had discontinued the study of which 3 subjects discontinued due to death (LRTI, septic shock, and tumour haemorrhage – see safety section), and 1 subject withdrew consent, 1 subject was lost to follow-up, and 1 subject was enrolled in another study.

Demographics: Subject demographics and key characteristics, except for age and weight, were generally balanced between the nirsevimab 50/100 mg (first season) and 200 mg groups (second season). The majority of subjects were males (65%).

At the time of dosing for RSV season 1, median age was 8.3 months (range 0.7 to 12.3) and median weight was 7.6 kg (range 2.9 to 11.2).

At the time of dosing for RSV season 2, median age was 17.9 months (range 12.0 to 23.9) and median weight was 9.85 kg (range 6.2 to 14.7).

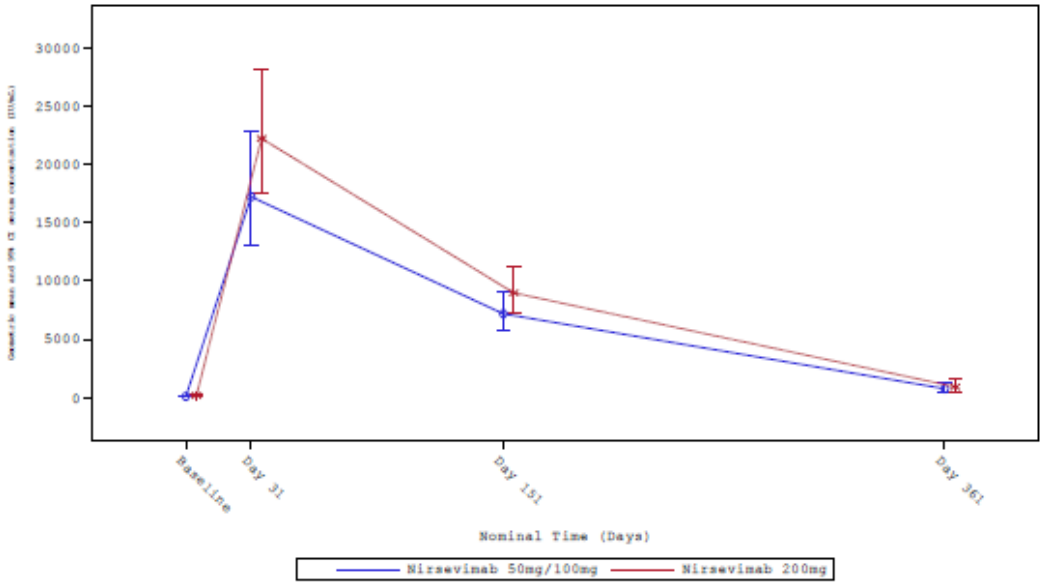
Immunocompromised conditions:

- Primary immunodeficiency: 33%
- HIV; 8%
- History of organ or bone marrow transplantation: 16%
- Immunosuppressive chemotherapy: 20%
- Systemic, high-dose corticosteroid therapy: 29%
- Other immunosuppressive therapy: 15.0%

Incidence of Medically Attended RSV Lower Respiratory Tract Infection: No events were observed during the first 150 days post treatment neither in the first or second RSV season. Three subjects experienced a MA RSV LRTI (although not protocol defined) between day 151 and 361 post treatment in the first RSV season and one of these children were hospitalised.

Serum concentrations: The serum concentrations at day 151 in the first RSV season are comparable to the serum concentrations observed in the MELODY study, where the same dose was used. But in the second RSV season, the exposure is around 50% higher due to the higher dose (Figure 29 and 30), which was also evident in the MEDLEY study.

Figure 29 **Geometric Mean Concentration (IU/mL) of Serum RSV Neutralising Antibodies (As-treated Population)**



CI = confidence interval; RSV = respiratory syncytial virus.
Source: Figure 14.4.2.1_a.

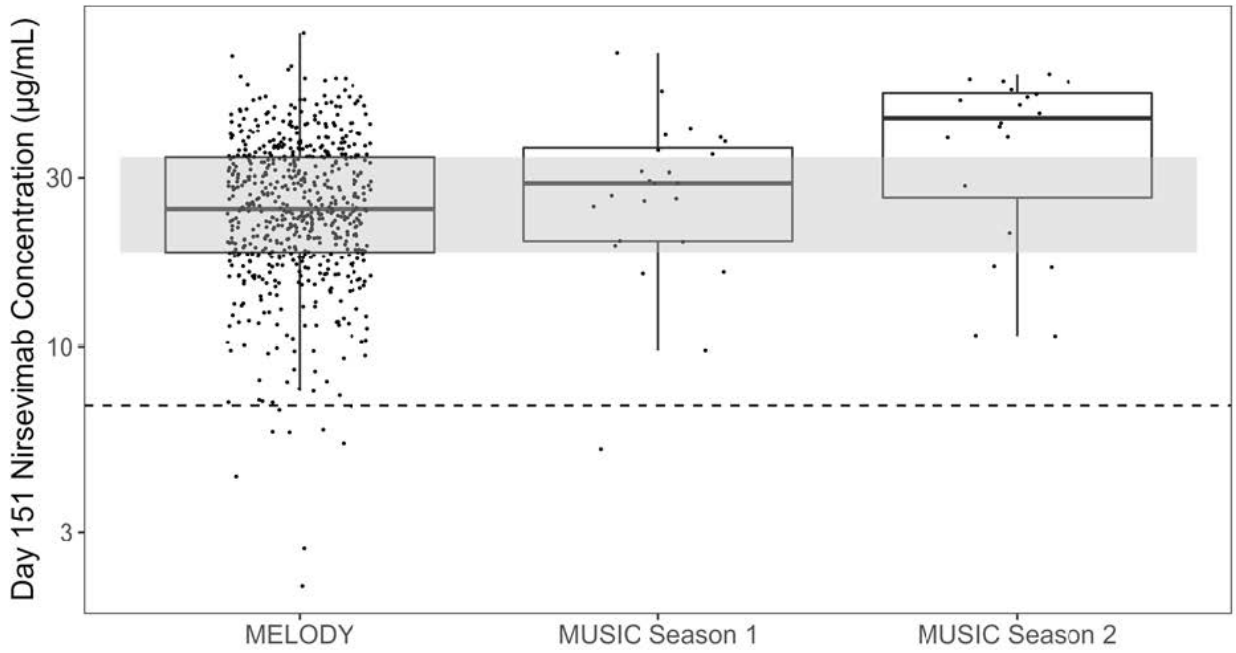
The MAH has observed 14 outliers which a rapid decline in serum concentrations. This is further addressed in the pharmacology section.

In 9 out of 14 of the subjects, protein loss was suspected to influence the rapid decline:

- One subject had nephrotic syndrome
- Three subjects had received bone marrow transplantation and were reported to have graft versus host disease, which is a potential cause of a protein loss enteropathy
- Five subjects were post liver transplantation. All had evidence of liver compromise at the start of, or during, the study. Chronic liver disease, with cirrhosis, portal hypertension or hepatic venous outflow obstruction may be associated with intestinal lymphangiectasia and excess protein loss.

In the remaining 5 subjects there was no clear documentation of a protein-losing condition.

Figure 30 Boxplots of Observed Day 151 Serum Concentrations in MUSIC Subjects Compared to MELODY



Day 151 concentrations are Visit Day 151 ± 14 days. Grey band is the reference inter-quartile range for MELODY Day 151 concentrations. The horizontal dashed black line is the nonclinical EC90 (6.8 µg/mL). Subject 4305001 (MUSIC) was dosed 100 mg at age 12.2 months (flagged as Season 2) but was included in Season 1 for extrapolation. Data presented are paediatric subjects who are < 5 kg receiving 50 mg or ≥ 5kg receiving 100 mg in Season 1 or receiving 200 mg in Season 2.

EC90 = 90% effective concentration.

Source: Figure 31, 2022 Population PK report, Module 5.3.3.5, this Variation.

ADA:

Eleven (11.3%) of the 97 subjects had treatment-emergent ADAs during the study. No effect on PK was identified through Day 151. On Day 361, a larger proportion of ADA-positive subjects had samples below the limit of quantification compared to ADA-negative subjects, indicating an influence of ADA on PK between Day 151 and Day 361. However, the numbers were small and therefore no conclusion of the impact of ADA on nirsevimab PK can be done. Please see the pharmacology section and safety section regarding ADA.

Further, 81.4% (48/59) of subjects were predicted to achieve exposures above the efficacious target (80.0% [28/35] in Season 1 and 83.3% [20/24] in Season 2), supporting protection from RSV disease in infants and children with immunocompromised conditions entering their first or second RSV.

For safety data, please refer to the safety section.

Data from all subjects followed for 361 days were available for assessment.

No events of medically attended RSV lower respiratory tract infection were observed during the first 150 days in season 1 or season 2 (primary follow-up period). During day 151-361 post treatment in the first RSV season, 3 subjects had an event, of which 1 child was hospitalised. No events were seen in the group of subjects dosed in their second season.

ADA:

Eleven (11.3%) of the 97 subjects had treatment-emergent ADAs during the study. No effect on PK was identified through Day 151, but on Day 361, a larger proportion of ADA-positive subjects had samples below the limit of quantification compared to ADA-negative subjects.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The Phase II/III randomised, double-blind, palivizumab-controlled study D5290C00005 (MEDLEY) was designed to evaluate the safety, PK, ADA, and efficacy (descriptive) of nirsevimab, in high risk children eligible to receive palivizumab when entering their first or second RSV season.

For season 1, MEDLEY subjects (preterm children and children with chronic lung disease (CLD) and congenital heart disease (CHD)) were randomised 2:1 to nirsevimab (50 mg or 100 mg and subsequently 4 monthly doses of placebo) or palivizumab 15mg/kg x 5 monthly.

The primary endpoint was safety, and secondary endpoints were pharmacokinetics and descriptive efficacy endpoints. In order to establish efficacy in children vulnerable to severe RSV infection, extrapolation was used from the MELODY trial (pivotal study in the initial approval). This approach was considered acceptable and is in accordance with the PIP.

To generate data for children entering their second RSV season, only the CLD/CHD cohort in MEDLEY continued into the second RSV season, where they received a second dose of nirsevimab (200 mg) or palivizumab (5 mg/kg (5 doses)). In addition, a phase II single-arm, open-label study (MUSIC) in immunocompromised patients was conducted in an RSV season 1 and 2. Hence the population for the second season of RSV were children vulnerable to severe RSV disease. This is reflected in the indication in the SmPC.

A 200 mg dose is proposed for the CLD and CHD patients entering their second RSV season. Taking into account the anticipated increase in body weight at the time for second RSV season treatment (8.5 to 15 kg), modelling suggests that the target exposure of AUC 12.8 day·mg/mL is achieved and maintained with a dose of 200 mg.

Efficacy endpoints were secondary endpoints in both the MEDLEY study and the MUSIC study. Those were MA LRTI and MA LRTI with hospitalisation through 150 days post first dose in season 2.

The design of the studies is considered adequate and is in accordance with the PIP.

Efficacy data and additional analyses

In total, 262 children from MEDLEY continued into the second season part of the trial (out of 306 dosed in season 1). The children that were randomised to nirsevimab in season 1, continued with nirsevimab in season 2 and the children that were randomised to palivizumab in the first season were re-randomised to either nirsevimab or palivizumab in their second RSV season.

As for season 1, efficacy is based on PK extrapolation including data from MELODY and Study 3. This is accepted and in accordance with the PIP. A target exposure (AUC0-∞) of 12.8 day*mg/mL was defined as the protective exposure threshold.

The PK model was updated and GoF plots and VPCs indicated that the final model could adequately describe nirsevimab PK. The updated Pop PK model was used to predict the data from MUSIC study in

immunocompromised children who received nirsevimab in Season 1 (n=35) and in Season 2 (n=24). The GoF plots and VPCs indicated the updated Pop PK model could describe the sparse data from MUSIC.

From the boxplots of predicted AUC365, Season 2 simulations performed for the few IC children in MUSIC seem to be enclosed within the predicted exposure ranges for the CHD and CLD subjects in MEDLEY that received a Season 2 treatment. It is noticeable that exposures seemed slightly higher in CLD subjects compared to CHD subjects and lowest in subjects with IC. For all subjects in MEDLEY that received a Season 2 dose (n=189), AUC365 ranged up to 41.9 day×mg/mL, which is almost twice the maximum exposure from studies D5290C00003, MELODY and MEDLEY Season 1.

Further simulations were carried out across the range of study weights/ages for a typical subject in virtual patients. For these simulations it was assumed that Season 2 subjects did not receive a Season 1 dose. However, this is not reflecting the SmPC recommendations where there are no restrictions to receive a Season 2 dose for infants not undergoing cardiac surgery. The 200 mg dose results in exposures almost twice the approved 50 and 100 mg Season 1 doses. The 2nd dose also results in a lower CL than expected from age and weight. The Applicant was requested to simulate “worst case” exposure-time profiles where a subject of 1 kg receive a 50 mg dose and a subject of 5 kg receive a 100 mg dose late in Season 1 and both receive a 200 mg dose early in Season 2 and discuss whether these scenarios could pose any safety concerns. An exposure within the range of the exposure seen in adults were observed, which is considered acceptable and no minimum time between season 1 and 2 is considered necessary to be included in the SmPC.

Safety data was collected for subjects who received Season 2 treatment from MEDLEY and MUSIC. In MEDLEY RSV Season 2, a total of 6 subjects weighed < 7 kg on Day 1 of RSV Season 2, of which 5 received the projected Season 2 treatment. Treatment emergent AEs were reported for all 5 subjects. Day 31 and Day 151 Season 2 serum concentrations from the 5 subjects in MEDLEY ranged from 154.07 µg/mL to 251.30 µg/mL at Day 31 and from 1.8 µg/mL to 84.08 µg/mL at Day 151. This is well above the mean serum concentration of 153.96 µg/mL at Day 31 (Season 2). Thus, it can be concluded that the 5 subjects with a body weight <7 kg who all experienced treatment emergent AEs following a Season 2 dose of 200 mg in the MEDLEY study, all experienced a higher than average exposure. The sample size is too small to confirm or rule out risk of treatment emergent AEs of RSV Season 2 treatment for infants with a body weight <7 kg.

The updated Pop PK model could capture the sparse data from Season 2 collected in MEDLEY and MUSIC from children with CLD, CHD or IC. The Season 2 dose gave rise to higher exposures in most subjects than the approved Season 1 treatment and the ADA incidents were low and did not seem persistent, thus there are no concerns regarding efficacy of the proposed Season 2 treatment from a modelling perspective.

In the MEDLEY study, there were no events of MA LRTI or MA LRTI with hospitalisation through 150 days post first dose in season 2 in any treatment group. The study population has almost completed the full follow-up period, and from day 151 to day 360 only 1 event has occurred, which was in the pal/nir treatment group. A number of secondary and exploratory endpoints were also evaluated. However, the results does not impact the efficacy evaluation (either low event numbers or less relevant for the indication).

In the MUSIC study that included immunocompromised subjects, no events of medically attended RSV lower respiratory tract infection were observed during the first 150 days in season 1 or season 2 (primary follow-up period). During day 151-361 post treatment in the first RSV season, 3 subjects had an event, of which 1 child was hospitalised. No events were seen in the group of subjects dosed in their second season.

Overall, the data from the MEDLEY study in children vulnerable to severe RSV disease together with the modelling and extrapolation of efficacy are supportive of the indication.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

Please refer to the above.

2.4.4. Conclusions on the clinical efficacy

In conclusion, in children vulnerable to RSV disease during their second season, the modelling and extrapolation of efficacy from the MELODY Study is supportive of the indication.

2.5. Clinical safety

Introduction

The original nirsevimab Marketing Authorisation Application clinical data package submitted 28 January 2022 (procedure EMEA/H/C/005304/0000) supported safety of nirsevimab for an indication to prevent RSV lower respiratory tract disease in all infants from birth who are entering their first RSV season. The nirsevimab clinical development programme includes a Phase I study in adults, a Phase Ib/IIa study in preterm infants, 3 complementary pivotal studies in infants and children, and an open-label study in immunocompromised infants and children.

Nirsevimab, a fully human mAb that binds the RSV F protein, has no endogenous target in humans. The nonclinical toxicology programme did not indicate any nirsevimab related safety concerns, and there was no cross-reactivity between nirsevimab and normal human tissues and selected juvenile neonatal and foetal tissues in tissue cross-reactivity studies. Thus, any potential risks defined for nirsevimab were based primarily on the generic safety risks associated with any immunoglobulin (including mAbs) and were the focus of safety assessments throughout the clinical programme. These included immediate hypersensitivity (including anaphylaxis) and immune complex disease. Thrombocytopaenia was also included as a potential risk as events of thrombocytopaenia were reported during post-approval use of palivizumab, a mAb with a similar mechanism of action as nirsevimab. These potential risks are AESIs for the clinical development programme.

This variation includes addendum safety data for children who received nirsevimab in RSV Season 2 in MEDLEY through at least 150 days post first dose (DCO date of 30 April 2022). The MEDLEY Season 2 Analysis also includes RSV Season 1 safety data through 360 days post dose for the preterm and CHD/CLD cohorts. Safety data are also presented for immunocompromised infants and children up to 24 months of age who have received nirsevimab in RSV Season 1 or 2 (with follow-up to 361 days post dose) in the open-label Study D5290C00008 (MUSIC). Safety data are currently available from 274

subjects dosed with nirsevimab in their second RSV season, including 220 subjects in the Phase II/III MEDLEY Study (ongoing) and 54 subjects in the open-label Phase II MUSIC Study. The MUSIC study also includes safety data for an additional 48 immunocompromised subjects dosed with nirsevimab in their first RSV season.

- Data on safety are presented from the MEDLEY Season 2 Analysis, conducted in those subjects from the Season 1 CLD/CHD cohort, who continued to Season 2. Subjects in the CLD/CHD cohort progressed into a second RSV season and received an additional dose of IP. All subjects who received nirsevimab in Season 1 received another dose of nirsevimab in Season 2 (NIRS/NIRS group; N = 180). Subjects who received palivizumab in Season 1 were re-randomised 1:1 to receive nirsevimab (PALI/NIRS group; N = 40) or palivizumab (PALI/PALI group; N = 42) in Season 2.

- Additional safety data are presented from 100 subjects dosed with nirsevimab in MUSIC. MUSIC recruited immunocompromised infants and children up to 24 months of age, who received the proposed dose of nirsevimab in Season 1 (50 or 100 mg) or Season 2 (200 mg); unlike MEDLEY subjects did not receive IP in 2 consecutive seasons.

Table 1. provides an overview of the design of these studies.

Table 22 **Studies Contributing to the Evaluation of the Clinical Safety of Nirsevimab for this Type II Variation**

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomised (dosed) by analysis
Ongoing				
D5290C00005 (MEDLEY) **Pivotal** • **RSV Season 1** (complete; all subjects followed up to Day 361). • **RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361). Study ongoing.	Phase II/III, randomised, double-blind, palivizumab-controlled (safety, descriptive efficacy, PK, and ADA).	Infants and children entering their first or second RSV season, eligible to receive palivizumab. **RSV Season 1:** Preterm infants born < 35 wGA (without CLD or CHD) (referred as preterm cohort) and term and preterm infants with CLD or CHD (referred as CLD/CHD cohort). **RSV Season 2:** Children ≥ 12 and ≤ 24 months with CLD or CHD (in CLD/CHD cohort) who received nirsevimab or palivizumab in RSV Season 1 25 countries, including US and Japan.	RSV Season 1 Nirsevimab: 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose followed by 4 once-monthly doses of IM placebo. Palivizumab: 15 mg/kg IM (5 once-monthly doses). RSV Season 2 Subjects in CLD/CHD cohort who received nirsevimab in Season 1, received 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo. Subjects in CLD/CHD cohort who received palivizumab in Season 1, received either 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo or palivizumab 15 mg/kg IM (5 once-monthly doses) in 1:1 re-randomised manner.	**Primary Analysis (Season 1)** [a] **Overall population** (comprised of preterm and CLD/CHD cohorts): • **Nirsevimab:** 616 (614), including 407 (406) in the preterm cohort + 209 (208) in the CLD/CHD cohort. • **Palivizumab:** 309 (304), including 208 (206) in the preterm cohort + 101 (98) in the CLD/CHD cohort. **Season 2 Analysis** [b] **CLD/CHD cohort:** • Nirsevimab/Nirsevimab [c]: 180 (180) • Palivizumab/nirsevimab [c]: 40 (40) • Palivizumab/palivizumab [c]: 42 (42)

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomised (dosed) by analysis
D5290C00008 (MUSIC) • **RSV Season 1 and RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361). Study ongoing.	Phase II, Open-label, uncontrolled, single-dose study (safety, descriptive efficacy, PK, and ADA)	Immunocompromised infants in their first year of life and entering their first RSV season at the time of dose administration, and children ≤ 24 months of age in their second year of life and entering their second RSV season at the time of dose administration. 6 countries, including US and Japan.	**1st year of life cohort:** **Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose **2nd year of life cohort:** **Nirsevimab:** 200 mg single IM dose	**Interim analysis:** [d] A total of 100 non-randomised, immunocompromised subjects who received the proposed dose of nirsevimab (46 subjects in the first year of life and 54 subjects in the second year of life).
Children dosed with nirsevimab in the second RSV season				274 [e]

[a] MEDLEY Primary Analysis (DCO 03 May 2021) was triggered when all randomised subjects in the overall population (preterm + CLD/CHD cohorts) had been followed up through at least 150 days post first dose in Season 1 and included all available safety, PK, ADA, and descriptive efficacy data. Safety data are now also available for subjects followed up through 360 days post dose in RSV Season 1 as reported in the MEDLEY iCSR 31 August 2022 and submitted in this second Type II variation; safety conclusions and profile are unchanged from the earlier DCO.

[b] Subjects from the MEDLEY CLD/CHD cohort only continued into a second RSV season and received a second course of IP. The MEDLEY Season 2 Analysis (DCO 30 April 2022) was triggered when all randomised subjects from the CLD/CHD cohort completed follow-up through at least 150 days post first dose in Season 2. The Season 2 Analysis included all available Season 1 data (through 360 days post first dose in Season 1) and Season 2 data (through at least 150 days post first dose in Season 2). All available safety, PK, ADA, and descriptive efficacy data at the time of the Season 2 Analysis data cut-off are reported in the MEDLEY iCSR 31 August 2022.

[c] For the MEDLEY Season 2 Analysis, the number of subjects randomised (dosed) is presented by 'Season 1 treatment/Season 2 treatment' (eg, 'PALI/NIRS' indicates that the subject was randomised to palivizumab in Season 1 and re-randomised to nirsevimab in Season 2).

[d] MUSIC 2nd Interim Analysis (DCO 19 September 2022) was triggered when all subjects were followed through 150 days post dose. All safety, PK, ADA, and descriptive efficacy data collected for these subjects were included in the 2nd Interim Analysis, as reported in the MUSIC iCSR 07 March 2023.

[e] Includes 2 subjects from MUSIC enrolled in the second year of life group (both age 12.3 months), who mistakenly received 50% of the full, planned dose (100 mg instead of 200 mg).

ADA = anti-drug antibodies; CHD = (haemodynamically significant) congenital heart disease; CLD = chronic lung disease (of prematurity); DCO = data cut-off; iCSR = interim clinical study report; IM = intramuscular; IP = investigative product; NIRS = nirsevimab; PALI = palivizumab; PK = pharmacokinetic(s); RSV = respiratory syncytial virus; US = United States; wGA = weeks gestational age.

Disposition

MEDLEY

All 262 subjects who continued into the Season 2 phase of the study were dosed (68.7%, 15.3%, and 16.0%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively). A total of 250 (95.4%) subjects (96.1%, 95.0%, and 92.9%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively), completed treatment (ie, did not discontinue IP). A total of 12 (4.6%) subjects (3.9%, 5.0%, and 7.1%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively), discontinued IP, with the main reason being withdrawal by the parent/guardian. No subjects discontinued from the MEDLEY study due to an AE, however three subjects in the NIRS/NIRS group, discontinued treatment due to 'other' reasons and two subjects in the NIRS/NIRS group discontinued IP due to 'other' reasons.

A total of 15 subjects (n = 6 nirsevimab, n = 7 palivizumab, n = 2 NIRS/NIRS) discontinued from the MEDLEY study due to “other reasons” and also included reasons like relocation and early termination. A total of 252 (96.2%) subjects (96.7%, 95.0%, and 95.2%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively), had completed follow-up through 150 days post first dose, and 104 (40.0%) subjects (38.3%, 45.0%, and 40.5%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively), had completed follow-up through 360 days post first dose (ie, reached Day 361 and completed Season 2). Two subjects in the NIRS/NIRS group discontinued IP due to ‘other’ reasons. No subjects discontinued from the study due to an AE.

MUSIC

In total, 106 subjects were screened, of which 6 (5.7%) subjects were screen failure; 100 subjects had been enrolled and dosed. Forty-eight (48.0%) subjects were enrolled and received 50 mg or 100 mg nirsevimab, and 52 (52.0%) subjects were enrolled and received 200 mg nirsevimab. Eighty-six (86.0%) subjects were enrolled at sites in the northern hemisphere, and 14 (14.0%) subjects were enrolled at sites in the southern hemisphere. At the time of dosing, 46 (46.0%) subjects were < 12 months of age and 54 (54.0%) subjects were ≥ 12 months of age.

In total, 6 (6.0%) subjects discontinued from the study; 3 (3.0%) subjects due to death (LRTI, septic shock, and tumour haemorrhage), 1 (1.0%) subject due to withdrawn consent, 1 (1.0%) subject was lost to follow-up, and 1 (10%) subject discontinued due to other reasons (the subject was enrolled in another clinical study and was therefore discontinued from this study by the Investigator). Ninety-four (94.0%) subjects had completed the Day 361 follow-up and completed the study.

Patient exposure

In MEDLEY (RSV Season 2), all subjects in the NIRS/NIRS (180/180) and PALI/NIRS (40/40) groups received at least one active dose and 90.5% of subjects in the PALI/PALI group (38/42) received at least 5 active doses. Across the 3 treatment groups, 96.2% of subjects had completed follow-up through 150 days post dose, and 39.7% of subjects had completed follow-up through 360 days post dose (ie, completed RSV Season 2).

In MUSIC, all subjects (100/100) received a single dose of nirsevimab. Forty-eight subjects were enrolled and received 50 mg or 100 mg nirsevimab, and 52 subjects were enrolled and received 200 mg nirsevimab.

Adverse events

MEDLEY (CLD/CHD Cohorts) in RSV Season 2

Adverse events were assessed in RSV Season 2 in MEDLEY in 262 of the subjects from the CLD/CHD cohort who continued in the study and received a second course of IP (200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo, or 5 once-monthly doses of palivizumab 15 mg) in RSV Season 2. Subjects were analysed in 3 treatment groups in RSV Season 2, NIRS/NIRS (n = 180), PALI/NIRS (n = 40), and PALI/PALI (n = 42), so named to indicate treatments received in Season 1 and Season 2 (Table 22).

In the MEDLEY study, overall the number of subjects with any TESAE were comparable across the treatment groups: (PALI/PALI (69.0%, N = 42), PALI/NIRS (72.5%, N = 40), NIRS/NIRS (70.0%, N = 180).

The numbers for ≥ 1 AESI based on selected MedDRA PT codes and ≥ 1 skin reaction, were comparable across treatment groups. Importantly there were no 1 IP-related event of ≥ Grade 3, no IP-related serious event, IP-related AESI based on selected MedDRA PT codes, no IP-related skin reaction.

The incidence of ≥ Grade 3 events was slightly higher in the NIRS/NIRS (7.8%) and PALI/NIRS groups (10.0%) vs the PALI/PALI group:(2.4%). The incidence of SAEs also was higher in the NIRS/NIRS (9.4%) and PALI/NIRS (10.0%) groups vs the PALI/PALI (0.0%) group for SAEs. The numerical differences incidences of SAEs between the treatment groups are predominantly driven by events in the SOC: infections and infestations. Numbers are small with regards to numeral imbalances.

Table 23 **Overall Summary of Treatment-emergent Adverse Events Through at Least 150 Days Post First Dose in Season 2 – As-treated Population – MEDLEY**

Subjects [a] with	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
≥ 1 event	29 (69.0)	29 (72.5)	126 (70.0)
Occurring ≤ 1 day post any dose	0 (0.0)	1 (2.5)	4 (2.2)
Occurring ≤ 3 days post any dose	5 (11.9)	8 (20.0)	22 (12.2)
Occurring ≤ 7 days post any dose	8 (19.0)	14 (35.0)	41 (22.8)
Occurring ≤ 14 days post any dose	18 (42.9)	15 (37.5)	76 (42.2)
≥ 1 IP-related event	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 event of ≥ Grade 3 [b]	1 (2.4)	4 (10.0)	14 (7.8)
Occurring ≤ 1 day post any dose	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤ 3 days post any dose	0 (0.0)	0 (0.0)	1 (0.6)
Occurring ≤ 7 days post any dose	0 (0.0)	0 (0.0)	2 (1.1)
Occurring ≤ 14 days post any dose	0 (0.0)	2 (5.0)	3 (1.7)
≥ 1 IP-related event of ≥ Grade 3 [b]	0 (0.0)	0 (0.0)	0 (0.0)
Any AE with outcome death	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 serious [c] event	0 (0.0)	4 (10.0)	17 (9.4)
≥ 1 serious [c] and/or ≥ Grade 3 [b] event	1 (2.4)	4 (10.0)	20 (11.1)
≥ 1 IP-related serious [c] event	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 AESI based on investigator assessments	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 AESI based on selected MedDRA PT codes	4 (9.5)	4 (10.0)	24 (13.3)
≥ 1 IP-related AESI based on sponsor-defined select MedDRA search criteria	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 IP-related skin reaction	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 NOCD	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 IP-related NOCD	0 (0.0)	0 (0.0)	0 (0.0)
≥ 1 event related to COVID-19	5 (11.9)	4 (10.0)	13 (7.2)
≥ 1 confirmed COVID-19 [d]	5 (11.9)	4 (10.0)	10 (5.6)
≥ 1 suspected COVID-19	0 (0.0)	0 (0.0)	3 (1.7)

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

[b] Grade 3: severe; Grade 4: life-threatening.

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

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

Treatment-emergent adverse events reporting period for Season 2 is from Season 2, Day 1 to Season 2, Day 361.
AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NIRS = nirsevimab; NOCD = new onset chronic disease; PALI = palivizumab; PT = preferred term.
Source: Table 14.3.2.1.1.2, Medley iCSR, Module 5.3.5.1.

Adverse Events by SOC and PT

Table 24 **Treatment-emergent Adverse Events in ≥ 3% of Subjects in Any Group by System Organ Class and Preferred Term Through at Least 150 Days Post First Dose in Season 2 (MEDLEY, As-treated Population)**

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Total number of TEAEs	118	120	534
Subjects with any TEAE	29 (69.0)	29 (72.5)	126 (70.0)
Gastrointestinal disorders	**11 (26.2)**	**9 (22.5)**	**32 (17.8)**
Diarrhoea	5 (11.9)	2 (5.0)	9 (5.0)

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Teething	2 (4.8)	0 (0.0)	7 (3.9)
Vomiting	3 (7.1)	3 (7.5)	6 (3.3)
Constipation	2 (4.8)	1 (2.5)	5 (2.8)
General disorders and administration site conditions	**5 (11.9)**	**8 (20.0)**	**22 (12.2)**
Pyrexia	5 (11.9)	8 (20.0)	21 (11.7)
Infections and infestations	**24 (57.1)**	**25 (62.5)**	**104 (57.8)**
Upper respiratory tract infection	7 (16.7)	7 (17.5)	45 (25.0)
Nasopharyngitis	9 (21.4)	6 (15.0)	22 (12.2)
Rhinitis	6 (14.3)	4 (10.0)	22 (12.2)
Viral upper respiratory tract infection	2 (4.8)	4 (10.0)	13 (7.2)
Gastroenteritis	2 (4.8)	1 (2.5)	12 (6.7)
COVID-19	3 (7.1)	3 (7.5)	9 (5.0)
Otitis media acute	2 (4.8)	4 (10.0)	8 (4.4)
Pharyngitis	0 (0.0)	2 (5.0)	8 (4.4)
Bronchiolitis	1 (2.4)	0 (0.0)	7 (3.9)
Conjunctivitis	2 (4.8)	1 (2.5)	7 (3.9)
Ear infection	3 (7.1)	2 (5.0)	6 (3.3)
Otitis media	0 (0.0)	3 (7.5)	5 (2.8)
Bronchitis	1 (2.4)	3 (7.5)	4 (2.2)
Lower respiratory tract infection	0 (0.0)	3 (7.5)	4 (2.2)
Injury, poisoning and procedural complications	**2 (4.8)**	**2 (5.0)**	**9 (5.0)**
Vaccination complication	2 (4.8)	0 (0.0)	1 (0.6)
Investigations	**3 (7.1)**	**5 (12.5)**	**8 (4.4)**
SARS-COV-2 test negative	1 (2.4)	3 (7.5)	4 (2.2)
SARS-COV-2 test positive	2 (4.8)	1 (2.5)	1 (0.6)
Nervous system disorders	**2 (4.8)**	**2 (5.0)**	**4 (2.2)**
Speech disorder developmental	2 (4.8)	1 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**3 (7.1)**	**7 (17.5)**	**31 (17.2)**
Rhinorrhoea	2 (4.8)	4 (10.0)	13 (7.2)
Skin and subcutaneous tissue disorders	**6 (14.3)**	**2 (5.0)**	**23 (12.8)**
Dermatitis diaper	1 (2.4)	0 (0.0)	8 (4.4)

[a] Number (%) of subjects with AEs, sorted alphabetically for SOC and frequency descending order for PT. Subjects with multiple events for the same PT were counted only once for each of those PTs. Subjects with events in > 1 PT were counted once for each of those PTs.

TEAEs reporting period for Season 2 is from Season 2 Day 1 to Season 2 Day 361.

AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; NIRS = nirsevimab; PALI = palivizumab; PT = preferred term; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: Table 14.3.2.1.2.2, MEDLEY iCSR 31 August 2022, Module 5.3.5.1.

Overall the number of subjects with any TEAEs by SOC and PT were comparable across the treatment groups: (PALI/PALI (69.0%, N = 42), PALI/NIRS (72.5%, N = 40), NIRS/NIRS (70.0%, N = 180).

Table 25 **Treatment-emergent Adverse Events in the Respiratory, Thoracic and Mediastinal Disorders System Organ Class by Preferred Term Through at Least 150 Days Post First Dose in Season 2 of MEDLEY – As-treated Population (Season 2)**

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Total number of TEAEs	118	120	534
Subjects with any TEAE	29 (69.0)	29 (72.5)	126 (70.0)
Respiratory, thoracic and mediastinal disorders	**3 (7.1)**	**7 (17.5)**	**31 (17.2)**
Rhinorrhoea	2 (4.8)	4 (10.0)	13 (7.2)
Bronchopulmonary dysplasia	0 (0.0)	0 (0.0)	4 (2.2)
Nasal congestion	0 (0.0)	1 (2.5)	4 (2.2)
Cough	0 (0.0)	0 (0.0)	3 (1.7)
Catarrh	0 (0.0)	0 (0.0)	2 (1.1)
Oropharyngeal pain	0 (0.0)	0 (0.0)	2 (1.1)
Adenoidal hypertrophy	0 (0.0)	1 (2.5)	1 (0.6)
Asthma	0 (0.0)	0 (0.0)	1 (0.6)
Bronchial hyperreactivity	0 (0.0)	0 (0.0)	1 (0.6)
Cough variant asthma	0 (0.0)	0 (0.0)	1 (0.6)
Pleural effusion	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonia aspiration	0 (0.0)	0 (0.0)	1 (0.6)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.6)
Rhinitis allergic	0 (0.0)	0 (0.0)	1 (0.6)
Tonsillar hypertrophy	0 (0.0)	0 (0.0)	1 (0.6)
Upper respiratory tract inflammation	0 (0.0)	0 (0.0)	1 (0.6)
Atelectasis	0 (0.0)	1 (2.5)	0 (0.0)
Nasal obstruction	1 (2.4)	0 (0.0)	0 (0.0)
Stridor	0 (0.0)	1 (2.5)	0 (0.0)
Wheezing	0 (0.0)	1 (2.5)	0 (0.0)

[a] Number (%) of subjects with AEs, sorted by frequency descending order for PT. Subjects with multiple events for the same PT were counted only once for each of those PTs. Subjects with events in > 1 PT were counted once for each of those PTs.

TEAEs reporting period for Season 2 is from Season 2, Day 1 to Season 2, Day 361.

AE = adverse event; iCSR = interim clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; NIRS = nirsevimab; PALI = palivizumab; PT = preferred term; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

The incidences of the SOC Respiratory, thoracic and mediastinal disorders were higher for the PALI/NIRS group (17.5%) and the NIRS/NIRS group (17.5%), compared to PALI/PALI group (7.1%).

The differences in frequencies among treatment groups were predominantly driven by events associated with the underlying comorbid condition of CLD/CHD or infections of the respiratory tract, and thus not likely to be related to IP.

Apart from rhinorrhoea (7.2% vs. 4.8%), bronchopulmonal dysplasia (2.2% vs. 0%), nasal congestion (2.2% vs. 0%) and cough (1.7% vs. 0%) in the NIRS/NIRS vs. PALI/PALI treatment groups, all other events were reported in ≤ 2 subjects.

By SOC and PT: CLD and CHD Populations

Table 26 **Overall Summary of Treatment-emergent Adverse Events in the CLD and CHD Subpopulations Through at Least 150 Days Post First Dose in Season 2 – As-treated Population (Season 2)**

Subjects [a] with	Number (%) of subjects					
	CLD			CHD		
	PALI/PALI (N = 32)	PALI/NIRS (N = 25)	NIRS/NIRS (N = 132)	PALI/PALI (N = 11)	PALI/NIRS (N = 14)	NIRS/NIRS (N = 56)
≥ 1 event	23 (71.9)	15 (60.0)	86 (65.2)	7 (63.6)	13 (92.9)	45 (80.4)
Occurring ≤1 day post any dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	4 (7.1)
Occurring ≤3 days post any dose	3 (9.4)	4 (16.0)	11 (8.3)	2 (18.2)	4 (28.6)	11 (19.6)
Occurring ≤7 days post any dose	4 (12.5)	6 (24.0)	25 (18.9)	4 (36.4)	8 (57.1)	17 (30.4)
Occurring ≤14 days post any dose	13 (40.6)	7 (28.0)	51 (38.6)	5 (45.5)	8 (57.1)	29 (51.8)
≥1 IP-related event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 event of ≥Grade 3 [b]	1 (3.1)	2 (8.0)	9 (6.8)	0 (0.0)	2 (14.3)	6 (10.7)
Occurring ≤1 day post any dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤3 days post any dose	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Occurring ≤7 days post any dose	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.8)
Occurring ≤14 days post any dose	0 (0.0)	1 (4.0)	1 (0.8)	0 (0.0)	1 (7.1)	2 (3.6)
≥1 IP-related event of ≥Grade 3 [b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any AE with outcome death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 serious [c] event	0 (0.0)	2 (8.0)	13 (9.8)	0 (0.0)	2 (14.3)	5 (8.9)
≥1 serious [c] or ≥Grade 3 [b] event	1 (3.1)	2 (8.0)	14 (10.6)	0 (0.0)	2 (14.3)	7 (12.5)
≥1 IP-related serious [c] event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 AESI based on investigator assessments	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 AESI based on selected MedDRA PT codes	3 (9.4)	1 (4.0)	13 (9.8)	1 (9.1)	3 (21.4)	13 (23.2)
≥1 IP-related AESI based on selected MedDRA PT codes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 IP-related skin reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 NOCD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 IP-related NOCD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 27 **Overall Summary of Treatment-emergent Adverse Events in the CLD and CHD Subpopulations Through at Least 150 Days Post First Dose in Season 2 – As-treated Population (Season 2)**

Subjects [a] with	Number (%) of subjects					
	CLD			CHD		
	PALI/PALI (N = 32)	PALI/NIRS (N = 25)	NIRS/NIRS (N = 132)	PALI/PALI (N = 11)	PALI/NIRS (N = 14)	NIRS/NIRS (N = 56)
≥1 event related to COVID-19	3 (9.4)	2 (8.0)	10 (7.6)	2 (18.2)	2 (14.3)	3 (5.4)
≥1 confirmed COVID-19 [d]	3 (9.4)	2 (8.0)	8 (6.1)	2 (18.2)	2 (14.3)	2 (3.6)
≥1 suspected COVID-19	0 (0.0)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	1 (1.8)

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

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

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

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

Treatment-emergent adverse events reporting period for Season 2 is from Season 2, Day 1 to Season 2, Day 361.
AE = adverse event; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; NIRS = nirsevimab; NOCD = new onset chronic disease; PALI = palivizumab; PT = preferred term.
Source: Table 14.3.2.1.1.2.

In the MEDLEY Study RSV Season 2, a relatively high proportion of subjects experienced ≥ 1 TEA in the CLD/CHD subpopulations through at least 150 days post first dose in Season 2. For the PALI/PALI, PALI/NIRS, and NIRS/NIRS groups these were; for the CLD 71.9% (n=32), 60% (n= 25), 65.2% (n=132) and CHD 63.6% (n=7), 92.9% (n=14), 80.4% (n=56), respectively. The CHD population, already vulnerable, appears to generally have a little higher percentage in the groups receiving IP, including TEAs ≥Grade 3 in the NIRS/NIRS group, where there were 10.7% (n=6) in the CHD subpopulation compared to 6.8% in the CLD subpopulation. Percentages were also higher in the NIRS/NIRS group for serious or ≥Grade 3 TEAs (12.5% (n=7) in the CHD group vs. 10.6% (n=14). The percentages in the PALI/PALI group were in comparison 3.1% (n=1) and 0%, respectively.

However, there were no IP-related TEAs of ≥Grade 3, no IP-related serious events, no IP-related AESI based on selected MedDRA PT codes, IP-related skin reactions and no IP-related NOCD.

By SOC and PT, the distribution across treatment groups were overall comparable; PALI/PALI 69% (n=42), PALI/NIRS 72.5% (n=40) and NIRS/NIRS 70.0% (n=180). Numbers were small and no any clinically meaningful trends can be concluded from the imbalances. The distribution of the SOC Infections and Infestations was also comparable (57.1%, 62.5% and 57.8% for PALI/PALI, PALI/NIRS and NIRS/NIRS respectively, though by the PT Upper Respiratory Tract infection, there was a higher percentage (25.0%) in the NIRS/NIRS group compared to PALI/PALI and PALI/NIRS groups where percentages were 1.5% and 17.5% respectively. The pattern of TEAs is generally in accordance with what was observed in RSV Season 1.

TEAS's by intensity

Table 28 **Treatment-emergent Adverse Events of Grade 3 or Higher Severity by System Organ Class Through at Least 150 Days Post First Dose in Season 2 (MEDLEY, As-treated Population)**

System organ class Preferred term (MedDRA v23.1)	Highest severity [b]	Number (%) of subjects [a]		
		PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Subjects with at least one event	Grade 3	1 (2.4)	4 (10.0)	13 (7.2)
	Grade 4	0 (0.0)	0 (0.0)	1 (0.6)
Cardiac disorders	**Grade 3**	**0 (0.0)**	**0 (0.0)**	**2 (1.1)**
Arrhythmia	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Atrioventricular block	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Cardiac failure	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Congenital, familial and genetic disorders	**Grade 4**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Fallots tetralogy	Grade 4	0 (0.0)	0 (0.0)	1 (0.6)

System organ class Preferred term (MedDRA v23.1)	Highest severity [b]	Number (%) of subjects [a]		
		PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Gastrointestinal disorders	**Grade 3**	**0 (0.0)**	**0 (0.0)**	**2 (1.1)**
Duodenal ulcer	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Intestinal obstruction	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
General disorders and administration site conditions	**Grade 3**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Pyrexia	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Infections and infestations	**Grade 3**	**1 (2.4)**	**4 (10.0)**	**10 (5.6)**
Upper respiratory tract infection	Grade 3	0 (0.0)	0 (0.0)	2 (1.1)
Nasopharyngitis	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Gastroenteritis	Grade 3	1 (2.4)	0 (0.0)	1 (0.6)
COVID-19	Grade 3	0 (0.0)	0 (0.0)	2 (1.1)
Otitis media acute	Grade 3	0 (0.0)	2 (5.0)	0 (0.0)
Ear infection	Grade 3	0 (0.0)	1 (2.5)	0 (0.0)
Lower respiratory tract infection	Grade 3	0 (0.0)	1 (2.5)	2 (1.1)
Bronchitis viral	Grade 3	0 (0.0)	0 (0.0)	2 (1.1)
Urinary tract infection	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Human herpesvirus 6 infection	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Rotavirus infection	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonia	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)
Bone abscess	Grade 3	0 (0.0)	1 (2.5)	0 (0.0)
Gastrointestinal infection	Grade 3	0 (0.0)	1 (2.5)	0 (0.0)
Mastoiditis	Grade 3	0 (0.0)	1 (2.5)	0 (0.0)
Vascular disorders	**Grade 3**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Cyanosis	Grade 3	0 (0.0)	0 (0.0)	1 (0.6)

[a] Number (%) of subjects with AEs sorted alphabetically for SOC and frequency descending order for PT. Subjects with multiple AEs in the same PT were counted only once in each of those PTs. Subjects with AE in more than one PT were counted once in each of those PTs.

[b] Grade 3: severe; Grade 4: life-threatening. Severity grade displayed if there is an occurrence in at least one group. Grade rows are not mandatory if there is no TEAE at certain PTs /grades.

TEAEs reporting period for Season 2 is from Season 2 Day 1 to Season 2 Day 361.

AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; NIRS = nirsevimab; PALI = palivizumab; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: Table 14.3.2.3.2, MEDLEY iCSR 31 August 2022, Module 5.3.5.1.

Treatment-emergent Adverse Events of Grade 3 or Higher Severity by System Organ Class Through at Least 150 Days Post First Dose in Season 2, were numerically higher in the NIRS/NIRS (7.2%) and PALI/NIRS (10.0%) groups compared to the PALI/PALI group (2.4%), mainly driven by the SOC Infections and Infestations. None of these TEAs were considered IP-related. There was only one Grade 4 event reported which was in the NIRS/NIRS group. Numbers a generally small and no trends of concern

can be concluded from the numerical imbalances. The pattern is in accordance with the safety described for RSV Season 1.

Adverse Events Related to Investigational Product

No IP-related TEAEs were reported in Season 2.

Adverse Events by Time Relative to Dosing

In the MEDLEY Study, Treatment-emergent AEs within 1- and 3-days post first dose in RSV Season 2 (Table 28), were few in the CLD/CHD Cohort, with a maximum of 2.5% (one subject) in the PALI/NIRS treatment group. The PT registered in the subject was rhinorrhoea. Treatment-emergent AEs within 7- and 14-days post first dose were generally comparable between the PALI/PALI and the NIRS/NIRS groups, being 4.8% (n=2/42) vs. 3.9% (n=7/180) and 21.4% (n=9/42) vs. 15.6% (n=28/180), though slightly fewer in the subjects receiving IP. No clinically meaningful patterns were disclosed by SOC and PT.

Table 29 **Treatment-emergent Adverse Events by System Organ Class and Preferred Term in ≥ 2 Subjects in Any Group by Time Relative to First Dose (MEDLEY, As-treated Population, Season 2)**

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]											
	Within 1 day			Within 3 days			Within 7 days			Within 14 days		
	PALI/ PALI (N = 42)	PALI/ NIRS (N = 40)	NIRS/ NIRS (N = 180)	PALI/ PALI (N = 42)	PALI/ NIRS (N = 40)	NIRS/ NIRS (N = 180)	PALI/ PALI (N = 42)	PALI/ NIRS (N = 40)	NIRS/ NIRS (N = 180)	PALI/ PALI (N = 42)	PALI/ NIRS (N = 40)	NIRS/ NIRS (N = 180)
Subjects with at least one event	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	1 (2.5)	4 (2.2)	2 (4.8)	4 (10.0)	7 (3.9)	9 (21.4)	4 (10.0)	28 (15.6)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**2 (4.8)**	**0 (0.0)**	**3 (1.7)**
Enteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	2 (1.1)
General disorders and administration site conditions	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**2 (1.1)**	**0 (0.0)**	**0 (0.0)**	**3 (1.7)**
Pyrexia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	2 (1.1)
Infections and infestations	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**	**2 (1.1)**	**1 (2.4)**	**2 (5.0)**	**4 (2.2)**	**5 (11.9)**	**2 (5.0)**	**20 (11.1)**
Upper respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.4)	0 (0.0)	3 (1.7)	2 (4.8)	1 (2.5)	8 (4.4)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	1 (2.4)	0 (0.0)	4 (2.2)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	3 (1.7)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (2.5)**	**0 (0.0)**	**0 (0.0)**	**2 (5.0)**	**0 (0.0)**	**1 (2.4)**	**2 (5.0)**	**3 (1.7)**
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)	1 (2.4)	1 (2.5)	2 (1.1)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**1 (2.4)**	**1 (2.5)**	**1 (0.6)**	**1 (2.4)**	**1 (2.5)**	**4 (2.2)**
Dermatitis diaper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	3 (1.7)

[a] Number (%) of subjects with AEs sorted alphabetically for SOC and frequency descending order for PT. Subjects with multiple AEs in the same PT were counted only once in each of those PTs. Subjects with AE in more than one PT were counted once in each of those PTs.

Treatment-emergent AEs reporting period for Season 2 was from Season 2 Day 1 to Season 2 Day 361.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; NIRS = nirsevimab; PALI = palivizumab; PT = preferred term; SOC = system organ class.

Source: Table 14.3.2.2.7.2, MEDLEY iCSR 31 August 2022, Module 5.3.5.1.

CLD and CHD Subpopulations

Overall in the MEDLEY study there was no clear clinically meaningful pattern of TEAs by SOC and PT by time relative to dosing across the treatment groups ion the CLD and CHD subpopulations. Within the first day of dosing there were two subjects with at least one TEA in the NIRS/NIRS group, and four subjects within day 3, none in the PALI/PALI group, primarily by the SOC Infections and infestations, however

within seven to fourteen days after dosing the numbers were comparable across the treatment groups. No apparent patterns can be deducted from these numerical imbalances.

MUSIC (Immunocompromised Infants) in RSV Season 1 or Season 2

Subjects in MUSIC (N = 100) received a first dose of nirsevimab in either RSV Season 1 or Season 2; no subjects received nirsevimab in successive seasons. Subjects in the first year of life received the 50/100 mg dose and subjects in the second year of life received the 200 mg dose, which provided comparable nirsevimab serum exposures in both groups. Safety data from MUSIC are therefore presented together for all 100 subjects from both RSV seasons (Table 29).

Table 30 **Overall Summary of Treatment-emergent Adverse Events (As-treated Population)**

Subjects [a] with	Number (%) of subjects (N = 100)
At least one event	81 (81.0)
Occurring within 1 day of IP administration	4 (4.0)
Occurring within 3 days of IP administration	9 (9.0)
Occurring within 7 days of IP administration	23 (23.0)
Occurring within 14 days of IP administration	34 (34.0)
Occurring within 30 days of IP administration	54 (54.0)
At least one IP-related event	6 (6.0)
At least one event of grade 3 severity [b] or higher	35 (35.0)
Occurring within 1 day of IP administration	0
Occurring within 3 days of IP administration	1 (1.0)
Occurring within 7 days of IP administration	6 (6.0)
Occurring within 14 days of IP administration	8 (8.0)
Occurring within 30 days of IP administration	11 (11.0)
At least one IP-related event of grade 3 severity [b] or higher	0
Any AE with outcome death (grade 5 severity [b])	3 (3.0)
At least one serious [c] event	32 (32.0)
At least one IP-related serious [c] event	0
At least one serious [c] event of grade 3 severity [b] or higher	31 (31.0)
At least one IP-related serious [c] event of grade 3 severity [b] or higher	0

Table 31 **Overall Summary of Treatment-emergent Adverse Events (As-treated Population)**

Subjects [a] with	Number (%) of subjects (N = 100)
At least one AESI based on investigator assessment	5 (5.0)
At least one IP-related AESI based on investigator assessment	1 (1.0)
At least one AESI based on selected MedDRA PT codes	29 (29.0)
At least one IP-related AESI based on selected MedDRA PT codes	2 (2.0)
At least one skin reaction	21 (21.0)
At least one IP-related skin reaction	3 (3.0)
At least one skin hypersensitivity reaction	5 (5.0)
At least one IP-related skin hypersensitivity reaction	1 (1.0)
At least one NOCD	0

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

[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal. If the same event occurred multiple times within a particular subject, the highest severity was reported.

[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation or prolongation of existing inpatient hospitalisation, persistent or significant disability/incapacity, important medical event.

Time relative to dosing of 'within 1 day' was defined as any event started on study day 1; 'within 3 days' was defined as any event started on study day ≤ 3; 'within 7 days' was defined as any event started on study day ≤ 7; 'within 14 days' was defined as any event started on study day ≤ 14; 'within 30 days' was defined as any event started on study day ≤ 30.

Percentages were based on the number of subjects N.

AESI = adverse event of special interest; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects as per actual dose administered; NOCD = new onset chronic disease; PT = preferred term.

Source: Table 14.3.1.1_a.

In the MUSIC Study, RSV Season 1 and 2, 81.0% (n=81/100) subjects experienced at least one TEAE. Of these 23.0% (n=23/100) occurred within 7 days of IP administration. In total, 35% (n=35/100) subjects experienced at least one serious event of Grade 3 severity or higher, however none were considered IP-related. There were three AEs with the outcome of death, that were not considered IP-related either. Five subjects experienced at least one AESI based on investigator assessment, but only one AESI was considered IP-related. Three subjects (3.0%) experienced at least one IP-related skin reaction, and one subject (1%) experienced an IP-related hypersensitivity reaction.

Overall, 81% of subjects experienced a TEAE (771TEAE's in 81 subjects). Not unexpectedly, these predominantly belonged to the SOCs of Infections and Infestations (73.0% (n=73/100)), of which 36% (n=33/100) were upper respiratory tract infection by PT.

Most TEAE's were mild, but 35% (n=35/100) were Grade 3, Most TEAE's were mild, but 35% (n=35/100) were Grade 3, and 7 subjects (7%, n=7/100)) experienced Grade 4 (n=4) and Grade 5 (n=3). TEAE's. In total there were 6 subjects (6%) with 8 mild IP-related TEAEs, of which 4 were pyrexia. None of the Grade 3-5 TEAE's were IP-related. TEAE's reported within 1 day of IP administration occurred in four subjects and were pyrexia (4%), abdominal pain (1%) and rash (1%). Overall, the safety pattern was in accordance with the safety profile for RSV Season 1.

Skin Reactions and Skin Hypersensitivity Reactions

In MEDLEY, RSV Season 2, there were a total of 31 (n=262) skin reactions (11.8%) with no apparent imbalances between palivizumab and nirsevimab. In the CHD subpopulation there were a higher percentage of subjects with any skin reaction in the all nirsevimab group (NIRS/NIRS) than in the all palivizumab group (PALI/PALI; 25 % vs. 9.1%. Even though there is an observed difference of more than 10% among treatment groups, for any skin reactions, the imbalances, when evaluated by parameters including; skin reactions by SOC and PT, severity of events, skin reactions by time relative to dosing and IP-related skin reactions, including lack of evidence for hypersensitivity attributable to nirsevimab, are not clinically meaningful. There were no reports of IP-related skin reactions (including skin hypersensitivity reactions) in any treatment group (NIRS/NIRS, PALI/NIRS, PALI/PALI).

In MUSIC there were treatment-emergent skin reactions in 21 subjects. Only one skin hypersensitivity reaction was considered IP-related, and the subject had no ADA detected post-baseline. It is of note that none of the subjects who developed treatment-emergent ADA responses experienced a skin hypersensitivity reaction.

Adverse Events of Special Interest

Treatment emergent AESI's were based on the selected MedDRA PT's for immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopaenia. See (Table 14.3.4.5.3) below:

In the MEDLEY study (across RSV Season 1 and 2) there was a higher incidence of hypersensitivity events including anaphylaxis in the NIRS/NIRS group vs. the PALI/PALI group (27.8% vs. 23.8%). In the category of thrombocytopenia there was likewise a slightly higher incidence of thrombocytopenia in the NIRS/NIRS group (3.9% vs. 2.4%). In the CHD subpopulation one subject (NIRS/NIRS) experienced an AESI of heparin-induced thrombocytopenia, however post baseline ADA was negative. Post-baseline ADA's were identified in subjects with hypersensitivity including anaphylaxis in 50% (n=2) in the PALI/PALI-, 0% (n=0), PALI/NIRS- and 22.2% (n=4) NIRS/NIRS treatment group, respectively. For subjects with thrombocytopenia, none in any treatment group were ADA-positive post baseline. All-over, the incidence of post-baseline ADA was similar between treatment groups (10% vs. 9.6% in the NIRS/NIRS and PALI/PALI treatment group respectively), and no safety concerns are anticipated in this regard.

Table 14.3.4.5.3 Treatment-emergent Adverse Events of Special Interest based on Selected MedDRA Preferred Terms by System Organ Class and Preferred Term (Season 1 + Season 2), As-treated Population (Season 2)

CLD/CHD Cohort System Organ Class Preferred Term (MedDRA version 23.1)	Number (%) of Subjects* Palivizumab/ Palivizumab (N=42)	 MEDI8897/ MEDI8897 (N=180)	 Total (N=222)
Total number of TEAEs	17	84	101
Subjects with any TEAE	11 (26.2)	54 (30.0)	65 (29.3)
Hypersensitivity, including anaphylaxis	10 (23.8)	50 (27.8)	60 (27.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.6)	1 (0.5)
Heparin-induced thrombocytopenia	0 (0.0)	1 (0.6)	1 (0.5)
Eye disorders	0 (0.0)	1 (0.6)	1 (0.5)
Eye allergy	0 (0.0)	1 (0.6)	1 (0.5)
General disorders and administration site conditions	0 (0.0)	3 (1.7)	3 (1.4)
Medical device site rash	0 (0.0)	1 (0.6)	1 (0.5)
Oedema	0 (0.0)	1 (0.6)	1 (0.5)
Vaccination site urticaria	0 (0.0)	1 (0.6)	1 (0.5)
Immune system disorders	0 (0.0)	1 (0.6)	1 (0.5)
Hypersensitivity	0 (0.0)	1 (0.6)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	3 (7.1)	11 (6.1)	14 (6.3)
Cough	2 (4.8)	7 (3.9)	9 (4.1)
Asthma	0 (0.0)	2 (1.1)	2 (0.9)
Bronchospasm	0 (0.0)	1 (0.6)	1 (0.5)

CHD = Congenital Heart Disease; CLD = Chronic Lung Disease.
* Number (%) of subjects with adverse events, sorted on alphabetical order for system organ class and frequency descending order for preferred term. Subjects with multiple events in the same preferred term are counted only once in each of those preferred term. Subjects with events in more than 1 preferred term are counted once in each of those preferred term.
Treatment-emergent adverse events reporting period for Season 1 + Season 2 is from Season 1, Day 1 to Season 2, Day 361.

In MUSIC, 5 (5.0%) subjects had an AESI based on investigator assessment, all of which were assessed as skin hypersensitivity events of Grade 1 severity and only one (the AE of erythema) was considered IP-related. There were two events of immune-complex disease, which was Grade ≤ 2 worsening of the underlying condition, juvenile idiopathic arthritis but both were ADA-negative post baseline. The aggravation of the underlying condition, juvenile idiopathic arthritis is not expected after treatment with nirsevimab, and were more likely due to alternating phases of the disease and/or exacerbation due to intrinsic/extrinsic factors other than nirsevimab treatment.

Serious adverse event / deaths / other significant events

Deaths

In the MEDLEY study, RSV season 2 there were no deaths. In the MUSIC study there were three deaths (LRTI (not due to RSV), septic shock and tumour haemorrhage) not considered IP related by investigator.

In addition, one subject (Subject 7807004) was enrolled and died from septic shock secondary to typhlitis and Stenotrophomonas bacteraemia without receiving IP.

Serious Adverse Events

MEDLEY Overall CLD / CHD Cohort

The frequency of TESAEs by SOC and PT for the CLD/CHD cohort in Season 2 is summarised in Table 11.

The incidence of SAEs was low overall and numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (9.4% vs 10.0% vs 0% for NIRS/NIRS, PALI/NIRS, and PALI/PALI, respectively), (PALI/NIRS group (8 TESAEs in 8 subjects (n=40) NIRS/NIRS group (22 TESAEs in 17 subjects (n=180), compared to the PALI/PALI group (0, n=42); however, this was not observed within all analysed time points through 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%, respectively) and Nervous system disorders (0% vs 2.5% vs 0%, respectively). The most common SAEs (≥ 2 subjects in any treatment group) reported were bronchitis viral (3 vs 0 vs 0 subjects, respectively), COVID-19 (2 vs 0 vs 0 subjects, respectively), gastroenteritis (2 vs 0 vs 0 subjects, respectively), lower respiratory tract infection (2 vs 1 vs 0 subjects, respectively), and upper respiratory tract infection (2 vs 0 vs 0 subjects, respectively). Numbers by PT were however small and in accordance with observations in RSV season 1. None of the SAEs was considered by the investigator to be IP related.

No subjects in any treatment group had an SAE within 7 days post first dose in Season 2. Within 30 days post first dose, 2.2%, 2.5%, and 0% of subjects in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively, had an SAE.

CLD and CHD Subpopulations

The frequency of TESAEs are summarised by SOC and PT for the CLD and CHD subpopulations in Season 2. The incidence of SAEs was generally low in treatment groups across the individual CLD and CHD subpopulations. In both subpopulations, the incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (9.8% vs 8.0% vs 0% for the CLD subpopulation and 8.9% vs 14.3% vs 0% for the CHD subpopulation, for NIRS/NIRS, PALI/NIRS, and PALI/PALI, respectively). The differences in incidences of SAEs between the treatment groups were predominantly driven by events in the SOC: infections and infestations and numbers were small when assessed by PT. None of the SAEs was considered by the investigator to be IP related.

Table 30 **Treatment-emergent Serious Adverse Events in Any Group by System Organ Class and Preferred Term for the CLD/CHD Cohort Through at Least 150 Days Post First Dose in Season 2 (MEDLEY, As-treated Population)**

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Total number of TESAEs	0	8	22
Subjects with any TESAE	0 (0.0)	4 (10.0)	17 (9.4)
Cardiac disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Arrhythmia	0 (0.0)	0 (0.0)	1 (0.6)
Congenital, familial and genetic disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Fallots tetralogy	0 (0.0)	0 (0.0)	1 (0.6)
Gastrointestinal disorders	**0 (0.0)**	**0 (0.0)**	**2 (1.1)**
Duodenal ulcer	0 (0.0)	0 (0.0)	1 (0.6)
Intestinal obstruction	0 (0.0)	0 (0.0)	1 (0.6)
Infections and infestations	**0 (0.0)**	**4 (10.0)**	**13 (7.2)**
Bronchitis viral	0 (0.0)	0 (0.0)	3 (1.7)
COVID-19	0 (0.0)	0 (0.0)	2 (1.1)
Gastroenteritis	0 (0.0)	0 (0.0)	2 (1.1)
Lower respiratory tract infection	0 (0.0)	1 (2.5)	2 (1.1)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	2 (1.1)
Pharyngitis	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.6)
Rotavirus infection	0 (0.0)	0 (0.0)	1 (0.6)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.6)
Bone abscess	0 (0.0)	1 (2.5)	0 (0.0)
Ear infection	0 (0.0)	1 (2.5)	0 (0.0)
Gastrointestinal infection	0 (0.0)	1 (2.5)	0 (0.0)
Mastoiditis	0 (0.0)	1 (2.5)	0 (0.0)
Otitis media	0 (0.0)	1 (2.5)	0 (0.0)
Otitis media acute	0 (0.0)	1 (2.5)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Failure to thrive	0 (0.0)	0 (0.0)	1 (0.6)
Nervous system disorders	**0 (0.0)**	**1 (2.5)**	**0 (0.0)**
Nystagmus	0 (0.0)	1 (2.5)	0 (0.0)

System organ class Preferred term (MedDRA v23.1)	Number (%) of subjects [a]		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
Renal and urinary disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Calculus urinary	0 (0.0)	0 (0.0)	1 (0.6)
Vascular disorders	**0 (0.0)**	**0 (0.0)**	**1 (0.6)**
Cyanosis	0 (0.0)	0 (0.0)	1 (0.6)

[a] Number (%) of subjects with AEs, sorted alphabetically for SOC and frequency descending order for PT. Subjects with multiple events for the same PT were counted only once for each of those PTs. Subjects with events in > 1 PT were counted once for each of those PTs.

TESAE reporting period for Season 2 was from Season 2 Day 1 to Season 2 Day 361.

AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; NIRS = nirsevimab; PALI = palivizumab; PT = preferred term; SOC = system organ class; TESAE = treatment-emergent serious adverse event.

Source: Table 14.3.3.1.2, MEDLEY iCSR 31 August 2022, Module 5.3.5.1.

MUSIC

Treatment-emergent SAE's by SOC, PT and time relative to dosing are shown in Table 31.

Table 32 **Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term and by Time Relative to Dosing (As-treated Population)**

System Organ Class Preferred Term	Number (%) of subjects [a] (N = 100)				
Time relative to dosing	**Within 1 day**	**Within 3 days**	**Within 7 days**	**Within 14 days**	**Within 30 days**
Total number of serious TEAEs	0	1	6	11	16
Subjects with any serious TEAE	0	1 (1.0)	6 (6.0)	8 (8.0)	10 (10.0)
Blood and lymphatic system disorders	0	0	0	1 (1.0)	1 (1.0)
Anaemia	0	0	0	1 (1.0)	1 (1.0)
Thrombocytopenia	0	0	0	1 (1.0)	1 (1.0)
Infections and infestations	0	1 (1.0)	5 (5.0)	6 (6.0)	7 (7.0)
Klebsiella sepsis	0	0	1 (1.0)	2 (2.0)	2 (2.0)
Lower respiratory tract infection	0	1 (1.0)	1 (1.0)	1 (1.0)	2 (2.0)
Candida sepsis	0	0	0	1 (1.0)	1 (1.0)
COVID-19	0	0	0	0	1 (1.0)
Enterobacter sepsis	0	0	1 (1.0)	1 (1.0)	1 (1.0)
Pneumonia	0	0	1 (1.0)	1 (1.0)	1 (1.0)
Pneumonia viral	0	0	0	0	1 (1.0)
Urethritis	0	0	1 (1.0)	1 (1.0)	1 (1.0)
Injury, poisoning and procedural complications	0	0	0	0	1 (1.0)
Iatrogenic injury	0	0	0	0	1 (1.0)
Nervous system disorders	0	0	1 (1.0)	1 (1.0)	1 (1.0)

Table 33 **Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term and by Time Relative to Dosing (As-treated Population)**

System Organ Class Preferred Term	Number (%) of subjects [a] (N = 100)				
Time relative to dosing	**Within 1 day**	**Within 3 days**	**Within 7 days**	**Within 14 days**	**Within 30 days**
Intracranial pressure increased	0	0	1 (1.0)	1 (1.0)	1 (1.0)
Renal and urinary disorders	0	0	0	1 (1.0)	1 (1.0)
Nephrotic syndrome	0	0	0	1 (1.0)	1 (1.0)

[a] Number (%) of subjects with adverse events, sorted alphabetically for system organ class and by decreasing frequency for preferred term.

Time relative to dosing of 'within 1 day' was defined as any event started on study day 1; 'within 3 days' was defined as any event started on study day ≤ 3; 'within 7 days' was defined as any event started on study day ≤ 7; 'within 14 days' was defined as any event started on study day ≤ 14; 'within 30 days' was defined as any event started on study day ≤ 30.

Subjects with multiple events in the same preferred term were counted only once in that preferred term. Subjects with events in more than one preferred term were counted once in each of those preferred terms.

Subjects with events in more than one preferred term within the same system organ class and reporting period were counted only once in that system organ class.

Percentages were based on the number of subjects N.

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects as per actual dose administered; TEAE = treatment-emergent adverse event.

Source: Table 14.3.1.2.1.1_a.

In the MUSIC Study, a total of 86 treatment-emergent SAE's was reported in 32 subjects, with a specific treatment-emergent SAE reported in a maximum of 5 subjects (5.0%) which was the case for COVID-19 and pneumonia. Treatment-emergent SAE's by SOC, PT and time relative to dosing were mainly in the SOC of Infections and infestations with a total of 7 within 30 days. There were no treatment emergent SAE's within 1 day of dosing and one within three days of dosing. This is considered acceptable given the study population consists of immunocompromised subjects. No safety concerns are raised.

Laboratory findings

Clinical laboratory data were collected only from sites in Japan in MEDLEY and MUSIC. And laboratory-related AEs by SOC and PT in the SOCs of Blood and lymphatic system disorders, Hepatobiliary disorders, Investigations, and Renal and urinary disorders were reviewed for haematologic parameters, renal, or hepatic dysfunction for all subjects.

In MEDLEY Season 2, evaluation of laboratory-associated AEs in the SOCs of Blood and lymphatic system disorders, Hepatobiliary disorders, Renal and urinary disorders, and Investigations showed a low percentage of subjects with AEs and no clinically meaningful imbalance between treatment groups overall or by PT.

In MUSIC, laboratory-associated AEs in these SOCs were consistent with those expected for a population of immunocompromised infants and children and were related to underlying conditions or treatment for these conditions (eg, chemotherapy) and no trends or safety signals were observed.

MEDLEY

In MEDLEY, clinical laboratory data were collected from 12 subjects in Season 2 (8 in the NIRS/NIRS group, 3 in the PALI/NIRS group, and 1 in the PALI/PALI group). In MEDLEY, no observations of concern were reported for laboratory parameters (general chemistry/haematology/hepatic). No grade 3 or 4 shifts were reported.

MUSIC

Clinical laboratory data were collected for 26 subjects. No trends or clinically meaningful changes from baseline in mean values for the laboratory parameters assessed. Two subjects (7.7%) experienced at least 2 grade shifts from baseline to worst toxicity in white blood cell (leukocyte) results: a shift from Grade 0 to Grade 4 in 1 (3.8%) subject and a shift from Grade 1 to Grade 3 in 1 (3.8%) subject. One subject (3.8%) experienced a Grade 3 platelet toxicity; 1 subject (3.8%) experienced a Grade 3 leukocyte toxicity, and 2 subjects (7.7%) experienced a Grade 4 leukocyte toxicity. A total of 3 subjects (all with underlying leukaemia) from the MUSIC study had multiple grade shifts (at least a 2-grade shift or Grade 3 or 4 clinical laboratory toxicity.

Table 14.3.4.1 Grade 3-4 clinical laboratory toxicities
as-treated Japan subpopulation

Lab category Lab test Worst[a] toxicity grade[b]	Number (%) of subjects Nirsevimab 50mg/100mg (N=15)	 Nirsevimab 200mg (N=11)	 Total (N=26)
Chemistry - General			
S-Creatinine, Enzymatic (umol/L)			
n	15	11	26
Grade 3	0	0	0
Grade 4	0	0	0
>= Grade 3	0	0	0
Complete Blood Count			
B-Hemoglobin (g/dL)			
n	15	11	26
Grade 3	0	0	0
Grade 4	0	0	0
>= Grade 3	0	0	0
B-Platelets, Particle Concentration (10^9/L)			
n	15	11	26
Grade 3	1 (6.7)	0	1 (3.8)
Grade 4	0	0	0
>= Grade 3	1 (6.7)	0	1 (3.8)

[a] Among post-baseline assessments. B = Blood. S = Serum.
[b] Toxicity grading based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1.
Laboratory data were collected for subjects from Japan per requirement of PMDA.
Percentages are based on the number of subjects N.
AIDS = acquired immune deficiency syndrome. PMDA = Pharmaceutical and medical device agency.

Table 14.3.4.1 Grade 3-4 clinical laboratory toxicities
as-treated Japan subpopulation

Lab category Lab test Worst[a] toxicity grade[b]	Number (%) of subjects Nirsevimab 50mg/100mg (N=15)	 Nirsevimab 200mg (N=11)	 Total (N=26)
Liver Function			
S-Alanine Aminotransferase (ukat/L)			
n	9	11	20
Grade 3	0	0	0
Grade 4	1 (6.7)	0	1 (3.8)
>= Grade 3	1 (6.7)	0	1 (3.8)
S-Aspartate Aminotransferase (ukat/L)			
n	15	11	26
Grade 3	1 (6.7)	0	1 (3.8)
Grade 4	0	0	0
>= Grade 3	1 (6.7)	0	1 (3.8)
S-Bilirubin, Total (umol/L)			
n	15	11	26
Grade 3	0	0	0
Grade 4	0	0	0
>= Grade 3	0	0	0
White Blood Cell with Differential			
B-Leucocytes, Particle Concentration (10^9/L)			
n	15	11	26
Grade 3	1 (6.7)	0	1 (3.8)
Grade 4	2 (13.3)	0	2 (7.7)
>= Grade 3	3 (20.0)	0	3 (11.5)

[a] Among post-baseline assessments. B = Blood. S = Serum.
[b] Toxicity grading based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1.
Laboratory data were collected for subjects from Japan per requirement of PMDA.
Percentages are based on the number of subjects N.
AIDS = acquired immune deficiency syndrome. PMDA = Pharmaceutical and medical device agency.

Two-grade worsening from baseline to worst toxicity grade was experienced by 1 subject (3.8%) in AST. One subject (3.8%) experienced a Grade 4 ALT toxicity, 1 subject (3.8%) experienced a Grade 3 AST

toxicity, and no subjects experienced a Grade 3 or 4 TBL toxicity. No subjects experienced a Grade 3 or 4 creatinine toxicity. No subject had ALT ≥ 3 × ULN or AST ≥ 3 × ULN and TBL ≥ 2 × ULN.

Narratives are provided for those subjects who experienced at least a 2-grade shift from baseline to worst toxicity grade in clinical laboratory parameters and for those subjects who had Grade 3 or 4 clinical laboratory toxicities. The incidence of laboratory-related AEs was low in the following SOCs: Blood and lymphatic system disorders (18.0% [18/100] of subjects), Hepatobiliary disorders (3.0% [3/100] of subjects), Investigations (9.0% [9/100] of subjects), and Renal and urinary disorders (4.0% [4/100] of subjects).

Immunogenicity

In MEDLEY RSV Season 2, a total of 180 subjects received a second dose of IP, and 87.8% (n=158/180) in the NIRS/NIRS group, had minimum one sample available for ADA assessment at Season 2 Day 151. In the CLD/CHD cohort, a total of 36.7% (n=66/180) subjects in the NIRS/NIRS group had available samples for ADA assessment at Season 2 Day 361. In the CLD/CHD cohort, ADA was detected in 1.1% (n=1/90) and 0.0% (n=0/158) subjects at Day 31 and Day 151, respectively. Only sparse data are available as yet at Day 361 (in 66 subjects), but importantly, no detectable ADA was found in Season 2 subjects with positive ADA in Season 1. All-over, post-baseline ADA against IP in RSV Season 2 was found in one subject (2.5% n=1/40). Importantly, there was no registration of IP related AEs, AESIs, or skin hypersensitivity through 360 days post IP administration.

In the MUSIC Study, interim CSR, a total of 4.1% of subjects (n=4/97) with available ADA-samples were positive, and had no registration of IP-related AEs, AESIs, or skin hypersensitivity. In the final CSR of the MUSIC study the ADA incidence was 11.3% (11/97 subjects). A total of two subjects, ADA-positive on day 361, experienced TEAEs, of which one was an IP-related TEAE of Grade 1 pyrexia occurring within 60 minutes of IP administration, and the other was a Grade 1 skin reaction (macular rash) on Day 361 considered non-related to IP.

Overall, ADA to nirsevimab were detected in only a small percentage of subjects and did not appear to have a discernible clinical effect; no evidence of ADA impact on safety was observed. The new data from MEDLEY RSV Season 2 and MUSIC are consistent with the mechanism of action of nirsevimab, which, as a fully human mAb, would not be expected to be immunogenic.

The CHMP noted though that the employed immunogenicity assay has limitations in detecting ADAs at early onset (prior to Day 361) in the presence of high concentrations of drug, therefore, the incidence of ADA might not have been conclusively determined. The impact on clearance of nirsevimab is uncertain. Subjects who were ADA positive at Day 361 had reduced nirsevimab concentrations at Day 361 compared to subjects who received nirsevimab and were ADA-negative. The impact of ADA on the efficacy of nirsevimab has not been determined.

The immunogenicity subsection is reflected in the section 5.1 of the SmPC accordingly.

Safety in special populations

MEDLEY Study: Body Weight < 7 kg on Season 2 Day 1

In MEDLEY a total of 6 subjects (4 in NIRS/NIRS, 1 in PALI/NIRS, and one in PALI/PALI) weighed < 7 kg on Season 2 Day 1, and in MUSIC, only one subject weighed < 7 kg. In MEDLEY, TEAEs were reported most frequently in the NIRS/NIRS group (n=4), compared to the PALI/NIRS (n=1), and PALI/PALI (n=0) treatment groups within the SOCs of infections and infestations and gastrointestinal disorders, of which

Grade 3 events were reported in 3 subjects in the NIRS/NIRS group and 1 subject in the PALI/NIRS group. None of the events were considered IP-related, and there were no AESIs, or ADA positive post baseline subjects reported among these. In MUSIC, one subject, receiving nirsevimab at visit Day 1 and in whom a Grade 3 pneumonia event reported within 7 days of receiving IP and Grade 3 LRTI event reported with 30 days of receiving IP.

MEDLEY CLD/CHD Subjects who Received Replacement Dose Following Bypass Surgery in RSV Season 2

In MEDLEY Study RSV Season 2, a total of two subjects in the NIRS/NIRS group received replacement dose of IP due to CP bypass surgery. Due to limited data, no safety signal was reported. Neither subject had any detectable post baseline ADA to nirsevimab with available assessments to at least 150 days post first dose. No adverse events were assessed as related to the IP by the investigator.

Discontinuation due to adverse events

In MEDLEY season 2, there were no reported discontinuations due to adverse events, (in MEDLEY season 1, one subject (0.2%), a 5.2-month-old male infant in the nirsevimab group discontinued permanently on Day 91 due to a Grade 1 rash assessed as a skin hypersensitivity event (AESI) after receiving a placebo dose and was resolved the same day. The infant had mistakenly received nirsevimab on Day 31 of RSV Season 1 and had no detectable ADA to nirsevimab post-baseline).

In MUSIC, discontinuations were not evaluated (due to single IP) but there were no discontinuations due to an AE in dosed. Three deaths occurred but was considered unrelated to the IP (one subject with an AE of lower respiratory tract infection, one subject with an AE of tumour haemorrhage, and one subject with septic shock).

Post marketing experience

Nirsevimab was approved in the EU on 31 October 2022 and in Great Britain on 07 November 2022. No post-marketing data are presented within this variation procedure.

2.5.1. Discussion on clinical safety

The MAH has submitted an addendum of safety data for nirsevimab to support the extension of indication to include children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Safety data has been submitted from the MEDLEY Season 2 study (n=262) and from the MUSIC study in immunocompromised children (n=100). Patient exposure to investigational product (IP) was 274 subjects in RSV season 2 (MEDLEY, n= 180 + 40 = 220 + MUSIC, n= 52), of whom 268 subjects received one dose of 200 mg IP. The data submitted for evaluation of safety in the applied extension of indication and the studies contributing to evaluation of clinical safety for nirsevimab are considered adequate. Overall, no new trends of concern were observed with regards to the safety data submitted.

In the MEDLEY Study RSV Season 2, overall, a relatively high proportion of subjects experienced ≥ 1 TEAE in the CLD/CHD subpopulations through at least 150 days post first dose in Season 2. For the PALI/PALI, PALI/NIRS, and NIRS/NIRS groups these were for the CLD 71.9% (n=32), 60% (n= 25), 65.2% (n=132) and CHD 63.6% (n=7), 92.9% (n=14), 80.4% (n=56), respectively. The CHD population, already vulnerable, appears to generally have a little higher percentage in the groups

receiving IP, including TEAs ≥Grade 3 in the NIRS/NIRS group, where there were 10.7% (n=6) in the CHD subpopulation compared to 6.8% in the CLD subpopulation. Percentages were also higher in the NIRS/NIRS group for serious or ≥Grade 3 TEAs (12.5% (n=7) in the CHD group vs. 10.6% (n=14). The percentages in the PALI/PALI group were in comparison 3.1% (n=1) and 0%, respectively. However, it should be noted that there were no IP-related TEAs of ≥Grade 3, no IP-related serious events, no IP-related AESI based on selected MedDRA PT codes, IP-related skin reactions and no IP-related NOCD.

By SOC and PT, the distribution across treatment groups were overall comparable. Numbers were small and no clinically meaningful trends can be concluded from the imbalances. The distribution of the SOC Infections and Infestations was also comparable, though by the PT Upper Respiratory Tract infection, there was a higher percentage (25.0%) in the NIRS/NIRS group compared to PALI/PALI and PALI/NIRS groups where percentages were 1.5% and 17.5% respectively. The incidence of SAEs also was higher in the NIRS/NIRS (9.4%) and PALI/NIRS (10.0%) groups vs the PALI/PALI (0.0%) group for SAEs. However, no causality could be established (no biological plausibility, late onset of event, and the fact that alternative explanations were available.

The pattern of TEAs is generally in accordance with what was observed in RSV Season 1 and no new safety concerns are raised. Treatment-emergent Adverse Events of Grade 3 or Higher Severity by System Organ Class Through at Least 150 Days Post First Dose in Season 2, were numerically higher in the NIRS/NIRS (7.2%) and PALI/NIRS (10.0%) groups compared to the PALI/PALI group (2.4%), mainly driven by the SOC Infections and Infestations. None of these TEAs were considered IP-related. There was only one Grade 4 event reported which was in the NIRS/NIRS group. Numbers a generally small and no trends of concern can be concluded from the numerical imbalances. The pattern is in accordance with the safety described for RSV Season 1, and no safety concerns are raised.

In the MEDLEY Study, Treatment-emergent AEs within 1- and 3-days post first dose in RSV Season 2, were few in the CLD/CHD Cohort, with a maximum of 2.5% (one subject) in the PALI/NIRS treatment group. The PT registered in the subject was rhinorrhoea. Treatment-emergent AEs within 7- and 14-days post first dose were generally comparable across treatment groups, though slightly fewer in the subjects receiving IP. No clinically meaningful patterns were disclosed by SOC and PT. No safety concerns are raised.

Overall, in the MEDLEY study there was no clear clinically meaningful pattern of TEAs by SOC and PT by time relative to dosing across the treatment groups ion the CLD and CHD subpopulations. No apparent patterns can be deducted from these numerical imbalances and no safety concerns are raised. In the MUSIC Study, RSV Season 1 and 2, 81.0% (n=81/100) subjects experienced at least one TEAE. Of these 23.0% (n=23/100) occurred within 7 days of IP administration. In total, 35% (n=35/100) subjects experienced at least one serious event of Grade 3 severity or higher, however none were considered IP-related. There were three AEs with the outcome of death, that were not considered IP-related either. Five subjects experienced at least one AESI based on investigator assessment, but only one AESI was considered IP-related. Three subjects (3.0%) experienced at least one IP-related skin reaction, and one subject (1%) experienced an IP-related hypersensitivity reaction. Overall, 81% of subjects experienced a TEAE (771 TEAE's in 81 subjects). Not unexpectedly, these predominantly belonged to the SOCs of Infections and Infestations (73.0% (n=73/100)), of which 36% (n=33/100) were upper respiratory tract infection by PT.

Most TEAE's were mild, but 35% (n=35/100) were Grade 3, Most TEAE's were mild, but 35% (n=35/100) were Grade 3, and 7 subjects (7%, n=7/100)) experienced Grade 4 (n=4) and Grade 5 (n=3). TEAE's. In total there were 6 subjects (6%) with 8 mild IP-related TEAEs, of which 4 were pyrexia. None of the Grade 3-5 TEAE's were IP-related. TEAE's reported within 1 day of IP administration occurred in four subjects and were pyrexia (4%), abdominal pain (1%) and rash (1%). Overall, the safety pattern was in

accordance with the safety profile for RSV Season 1, and acceptable, bearing in mind that the study cohort in this case, comprised immunocompromised subjects.

With regards to Skin Reactions and Skin Hypersensitivity Reactions in MEDLEY, RSV Season 2, there were a total of 31 (n=262) skin reactions (11.8%) with no apparent imbalances between palivizumab and nirsevimab. In the CHD subpopulation there were a higher percentage of subjects with any skin reaction in the-all nirsevimab group (NIRS/NIRS) than in the-all palivizumab group (PALI/PALI; 25 % vs. 9.1%. There were no reports of IP-related skin reactions (including skin hypersensitivity reactions) in any treatment group. Even though there is an observed difference of more than 10% among treatment groups, for any skin reactions, it is acknowledged that the imbalances are not clinically meaningful, when evaluated by parameters including skin reactions by SOC and PT, severity of events, skin reactions by time relative to dosing and IP-related skin reactions, including lack of evidence for hypersensitivity attributable to nirsevimab. In MUSIC treatment-emergent skin reactions in 21 subjects. Only one skin hypersensitivity reaction was considered IP-related, and the subject had no ADA detected post-baseline. It is of note that none of the subjects who developed treatment-emergent ADA responses experienced a skin hypersensitivity reaction. Overall, no concerns for safety regarding hypersensitivity reactions is MEDLEY or MUSIC in RSV Season 2 are evident.

Treatment emergent AESI's were based on the selected MedDRA preferred terms (PTs) for immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopaenia. In the MEDLEY study (across RSV Season 1 and 2) there was a higher incidence of hypersensitivity events including anaphylaxis in the NIRS/NIRS group vs. the PALI/PALI group (27.8% vs. 23.8%). In the category of thrombocytopenia there was likewise a slightly higher incidence of thrombocytopenia in the NIRS/NIRS group (3.9% vs. 2.4%). In the CHD subpopulation one subject (NIRS/NIRS) experienced an AESI of heparin-induced thrombocytopenia, however post baseline ADA was negative. Post-baseline ADAs were identified in subjects with hypersensitivity including anaphylaxis in 50% (n=2) in the PALI/PALI-, 0% (n=0), PALI/NIRS- and 22.2% (n=4) NIRS/NIRS treatment group, respectively. For subjects with thrombocytopenia, none in any treatment group were ADA-positive post baseline. No clinically meaningful trends can be concluded upon, and no concerns for safety are raised. All-over, the incidence of post-baseline ADA was similar between treatment groups (10% vs. 9.6% in the NIRS/NIRS and PALI/PALI treatment group respectively), so no safety concerns are anticipated in this regard. In the MUSIC study there were two events of immune-complex disease, but both were ADA-negative post baseline. There were two events of immune-complex disease, which was Grade ≤ 2 worsening of the underlying condition, juvenile idiopathic arthritis but both were ADA-negative post baseline. The aggravation of the underlying condition, juvenile idiopathic arthritis is not expected after treatment with nirsevimab and were more likely due to alternating phases of the disease and/or exacerbation due to intrinsic/extrinsic factors other than nirsevimab treatment.

In the MEDLEY study, RSV season 2 there were no AEs with the outcome of death. In the MUSIC study there were two deaths (LRTI not due to RSV and tumour haemorrhage) not considered IP related by investigator. No safety concerns are raised with regards to deaths. In the MEDLEY study there were numerically more treatment-emergent serious adverse events in the PALI/NIRS group (8 TESAEs in 8 subjects (n=40) and the NIRS/NIRS group (22 TESAEs in 17 subjects (n=180), compared to the PALI/PALI group (0, n=42), most profound in SOC of Infections and infestations. The incidence of SAEs also was higher in the NIRS/NIRS (9.4%) and PALI/NIRS (10.0%) groups vs the PALI/PALI (0.0%) group for SAEs. However, no causality could be established (no biological plausibility, late onset of event (majority of these events was > 30 days post first dose), and the fact that alternative explanations were available. The same pattern was observed in the CLD and CHD subpopulations. Numbers by PT were however small and in accordance with observations in RSV season 1. All treatment emergent TESAEs were considered not related to the IP by the investigator. This is acceptable and no safety concerns are raised.

In MEDLEY, clinical laboratory data were collected from 12 subjects in Season 2, no observations of concern were reported for laboratory parameters (general chemistry/haematology/hepatic). No grade 3 or 4 shifts were reported. In MUSIC, clinical laboratory data were collected from 26 subjects. In subjects dosed with 50/100 mg IP, 1 subject experienced a Grade 3 shift in platelet counts, 1 subject a Grade 3 shift in AST and 1 and 2 subjects a Grade 3, and Grade 4 shifts in Leucocytes, respectively. A total, 3 subjects (all with underlying leukaemia) from the MUSIC study had multiple grade shifts (at least a 2-grade shift or Grade 3 or 4 clinical laboratory toxicity).

No new ADR's were identified in the MEDLEY Study (preterm infants and infants and children up to 24 months of age with CHD or CLD, compared to palivizumab) or in the open-label MUSIC Study (in immunocompromised infants up to 24 months of age). With regards to safety in special populations, in the MEDLEY Study, 6 subjects weighed < 7 kg on Season 2 Day 1, hereof 4 in the NIRS/NIRS group. These 4 subjects reported 23 TEAEs in total, predominantly in the SOC's of infections and infestations and (4 subjects) Gastrointestinal disorders (4 subjects). Three of the subjects experienced Grade 3 TEAEs. None of the TEAEs were considered IP-related. None were AESIs, and none were ADA positive post baseline. It is acknowledged that no exposure-dependent safety relationship for nirsevimab would be anticipated given the MOA, an no clear causality between events and IP can be concluded upon.

Regarding immunogenicity, in MEDLEY RSV Season 2, a total of 180 subjects received a second dose of IP, and 87.8% (n=158/180) in the NIRS/NIRS group, had minimum one sample available for ADA assessment at Season 2 Day 151. In the CLD/CHD cohort, a total of 36.7% (n=66/180) subjects in the NIRS/NIRS group had available samples for ADA assessment at Season 2 Day 361. In the CLD/CHD cohort, ADA was detected in 1.1% (n=1/90) and 0.0% (n=0/158) subjects at Day 31 and Day 151, respectively. Only sparse data are available as yet at Day 361 (in 66 subjects), but importantly, no detectable ADA was found in Season 2 subjects with positive ADA in Season 1. All-over, post-baseline ADA against IP in RSV Season 2 was found in one subject (2.5% n=1/40). Importantly, there was no registration of IP related AEs, AESIs, or skin hypersensitivity through 360 days post IP administration. In the MUSIC Study, interim CSR, a total of 4.1% of subjects (n=4/97) with available ADA-samples were positive, and had no registration of IP-related AEs, AESIs, or skin hypersensitivity. In the final CSR of the MUSIC study the ADA incidence was 11.3% (11/97 subjects). A total of two subjects, ADA-positive on day 361, experienced TEAEs, of which one was an IP-related TEAE of Grade 1 pyrexia occurring within 60 minutes of IP administration, and the other was a Grade 1 skin reaction (macular rash) on Day 361 considered non-related to IP.

Evaluation of immunogenicity raises no apparent safety concerns after administration of a second dose of nirsevimab.

In MEDLEY season 2, there were no reported discontinuations due to adverse events, and in MUSIC, discontinuations were not evaluated (due to single IP) but there were no discontinuations due to an AE in dosed. No post-marketing data were available at submission of the variation and are thus none are presented. This is acceptable for this procedure.

Additional expert consultations

None

2.5.2. Conclusions on clinical safety

Overall, the safety profile of nirsevimab is adequately characterised, and generally in accordance with the safety profile for RSV Season 1. No new adverse drug reactions have been reported.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The RMP is updated to include information to support the use of nirsevimab for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season and updates to the exposure table. The main proposed RMP changes as summarised by the MAH were the following:

RMP changes as summarised by the MAH were the following:

Part I	Updated to include information related to extended indication (use of nirsevimab for children up to 24 months of age who remain vulnerable to severe RSV disease in their second RSV season) including dosage and editorial updates.
Part II SI:	No updates
Part II SII:	No updates
Part II SIII:	Updated clinical trial exposure.
Part II SIV:	Updated special populations included or not included in clinical development program.
Part II SV:	No updates
Part II SVI:	No updates
Part II SVII:	No updates
Part II SVIII:	No updates
Part III:	No updates
Part IV	No updates
Part V	No updates
Part VI	Editorial updates

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version is acceptable.

The CHMP endorsed the Risk Management Plan version 2.3 (pursuant to variation II/018G) with the following content:

Safety concerns

Summary of safety concerns as proposed by the MAH in the updated RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance plan

Routine pharmacovigilance activities

MAH undertakes routine pharmacovigilance activities consistent with the ICH E2E Pharmacovigilance Planning Guideline. Routine pharmacovigilance activities (as defined by standard operating procedures and guidelines) are designed to rapidly assess the ongoing safety profile of nirsevimab throughout clinical development and in the post-authorisation period in order to characterise and communicate pertinent safety data appropriately. A comprehensive description of all aspects of the pharmacovigilance system is provided in the Pharmacovigilance System Master File, which is available upon request.

Specific adverse reaction follow-up questionnaires:

There are no follow-up questionnaires for safety concerns for nirsevimab. However, there are follow-up questionnaires in place for thrombocytopaenia.

Other forms of routine pharmacovigilance activities:

Continuous and thorough reviews of thrombocytopaenia as an AESI will be conducted as part of the close monitoring of this topic. Data from these reviews will be summarised in the PSURs.

Additional pharmacovigilance activities

Not applicable

Summary table of additional pharmacovigilance activities

The following additional pharmacovigilance activities planned for nirsevimab are shown in Table 3-1.

Table 3-1 Ongoing and Planned Additional Pharmacovigilance Activities

Study [Status]	Summary of objectives	Safety concerns addressed	Milestones	Due dates for EMA
Category 1 - Not applicable				
Category 2 – Not applicable				
Category 3 – Not applicable				

Risk minimisation measures

The MAH proposes no changes to the risk minimisation measures, which is endorsed.

Part VI: Summary of the risk management plan

The MAH has updated this section to include the claimed indication.

2.7. Update of the Product information

As consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated, together with sections 6.6 (instructions for administration) and 7 (change of MAH). The Package Leaflet is updated accordingly. Also, Annex II and IIIA (labelling) are amended (change in address details).

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Czechia, France, Italia, Malta and The Netherlands

2.7.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Beyfortus (nirsevimab) is included in the additional monitoring list as it contains a new active substance which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring (since receiving MA in 2022) and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

Respiratory syncytial virus is the most common cause of LRTI among infants and young children globally and is a major cause of hospital admission, with an estimated 33 million clinical cases and 3.6 million hospitalisations in children < 5 years of age globally in 2019 (Li et al 2022). This risk extends into the second RSV season, with an RSV-attributable hospitalisation rate for respiratory disease of approximately 2.5 per 1000 population estimated in children aged 6 to 23 months in the UK between 1995 and 2009 (Taylor et al 2016).

Beyfortus was approved in the EU on 31 October 2022 for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.

This variation provides data for infants and children with CLD or CHD who received nirsevimab in their second RSV season.

The following wording was proposed for the SmPC:

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

1 Neonates and infants during their first RSV season.

2 Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include but is not limited to children with:

- *Chronic lung disease of prematurity*
- *Haemodynamically significant congenital heart disease*
- *Immunocompromised states*
- *Down syndrome*
- *Cystic fibrosis*
- *Neuromuscular disease*
- *Congenital airway anomalies.*

Beyfortus should be used in accordance with official recommendations.

However, during the review the indication has been updated to the following:

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

i. Neonates and infants during their first RSV season.

ii. Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season (see section 5.1).

Beyfortus should be used in accordance with official recommendations

3.1.2. Available therapies and unmet medical need

The only currently approved prophylaxis for RSV for children vulnerable to severe disease in their second season is palivizumab (SYNAGIS®; EU approval 1999), a humanised RSV mAb directed against the F protein of RSV (Johnson et al 1997).

The licence for palivizumab includes children < 2 years of age with CLD of prematurity or haemodynamically significant CHD (Synagis US PI 2020, Synagis SmPC 2021). However, in addition to being limited to this patient population, palivizumab must be administered monthly by IM injection throughout the RSV season; the burden of monthly healthcare visits can be a barrier to compliance, thus diminishing the benefits of palivizumab, even in eligible children (Wong et al 2018)

3.1.3. Main clinical studies

Table 34 **Studies Contributing to the Nirsevimab Clinical Package for this Variation**

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomised (dosed) by analysis
Ongoing				
D5290C00005 (MEDLEY) **Pivotal** • **RSV Season 1** (complete; all subjects followed up to Day 361). • **RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361). Study ongoing.	Phase II/III, randomised, double-blind, palivizumab-controlled (safety, descriptive efficacy, PK, and ADA).	Infants and children entering their first or second RSV season, eligible to receive palivizumab. **RSV Season 1:** Preterm infants born < 35 wGA (without CLD or CHD) (referred as preterm cohort) and term and preterm infants with CLD or CHD (referred as CLD/CHD cohort). **RSV Season 2:** Children ≥ 12 and ≤ 24 months with CLD or CHD (in CLD/CHD cohort) who received nirsevimab or palivizumab in RSV Season 1 25 countries, including US and Japan.	**RSV Season 1** **Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose followed by 4 once-monthly doses of IM placebo. **Palivizumab**: 15 mg/kg IM (5 once-monthly doses). **RSV Season 2** Subjects in CLD/CHD cohort who received nirsevimab in Season 1, received 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo. Subjects in CLD/CHD cohort who received palivizumab in Season 1, received either 200 mg nirsevimab single IM dose followed by 4 once-monthly doses of IM placebo or palivizumab 15 mg/kg IM (5 once-monthly doses) in 1:1 re-randomised manner.	**Primary Analysis (Season 1)** [a] **Overall population** (comprised of preterm and CLD/CHD cohorts): • **Nirsevimab:** 616 (614), including 407 (406) in the preterm cohort + 209 (208) in the CLD/CHD cohort • **Palivizumab:** 309 (304), including 208 (206) in the preterm cohort + 101 (98) in the CLD/CHD cohort. **Season 2 Analysis** [b] **CLD/CHD cohort:** • Nirsevimab/Nirsevimab [c]: 180 (180) • Palivizumab/Nirsevimab [c]: 40 (40) • Palivizumab/palivizumab [c]: 42 (42)
D5290C00008 (MUSIC) • **RSV Season 1 and RSV Season 2** (all subjects followed up to at least Day 151; follow-up ongoing to Day 361). Study ongoing.	Phase II, Open-label, uncontrolled, single-dose study (safety, descriptive efficacy, PK, and ADA)	Immunocompromised infants in their first year of life and entering their first RSV season at the time of dose administration, and children ≤ 24 months of age in their second year of life and entering their second RSV season at the time of dose administration. 6 countries, including US and Japan.	**1st year of life cohort:** **Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose **2nd year of life cohort:** **Nirsevimab:** 200 mg single IM dose	**Interim analysis:** [d] A total of 100 non-randomised, immunocompromised subjects who received the proposed dose of nirsevimab (46 subjects in the first year of life and 54 [e] subjects in the second year of life).

[a] MEDLEY Primary Analysis (DCO 03 May 2021) was triggered when all randomised subjects in the overall population (preterm + CLD/CHD cohorts) had been followed up through at least 150 days post first dose in Season 1 and included all available safety, PK, ADA, and descriptive efficacy data. Safety data are now also available for subjects followed up through 360 days post dose in RSV Season 1 (DCO 30 April 2022), as reported in the MEDLEY iCSR dated 31 August 2022 and submitted in this second Type II variation; safety conclusions and profile are unchanged from the earlier DCO.

[b] Subjects from the MEDLEY CLD/CHD cohort only continued into a second RSV season and received a second course of IP. The MEDLEY Season 2 Analysis (DCO 30 Apr 2022) was triggered when all randomised subjects from the CLD/CHD cohort completed follow-up through at least 150 days post first dose in Season 2. The Season 2 Analysis included all available Season 1 data (through 360 days post first dose in Season 1) and Season 2 data (through at least 150 days post first dose in Season 2). All available safety, PK, ADA, and descriptive efficacy data at the time of the Season 2 Analysis data cut-off are reported in the MEDLEY iCSR.

[c] For the MEDLEY Season 2 Analysis, the number of subjects randomised (dosed) is presented by 'Season 1 treatment/Season 2 treatment' (eg, 'PALI/NIRS' indicates that the subject was randomised to palivizumab in Season 1 and re-randomised to nirsevimab in Season 2).

[d] This MUSIC interim analysis (DCO 19 September 2022) was triggered when all subjects were followed through 150 days post dose. All safety, PK, ADA, and descriptive efficacy data collected for these subjects were included in the 2nd Interim Analysis, as reported in the MUSIC 07 March 2023.

[e] Includes 2 subjects enrolled in the second year of life group (both aged 12.3 months), who mistakenly received 50% of the full, planned dose (100 mg instead of 200 mg).

ADA = anti-drug antibodies; CHD = (haemodynamically significant) congenital heart disease; CLD = chronic lung disease (of prematurity); DCO = data cut-off; iCSR = interim clinical study report; IM = intramuscular; IP = investigational product; NIRS = nirsevimab; PALI = palivizumab; PK = pharmacokinetic(s); RSV = respiratory syncytial virus; US = United States; wGA = weeks gestational age.

3.2. Favourable effects

The efficacy of nirsevimab in the MEDLEY and MUSIC study population was assessed by PK extrapolation, an approach to which the CHMP agreed.

The efficacy of nirsevimab in vulnerable children entering their second RSV season is based on PK data from the MEDLEY study which included children < 24 months of age with congenital heart disease or chronic lung disease and extrapolation of efficacy from the MELODY study which included healthy children entering their first RSV season.

A 200 mg dose is proposed for the CLD and CHD patients entering their second RSV season. Taking into account the anticipated increase in body weight at the time for second RSV season treatment (8.5 to 15 kg), modelling suggests that the target exposure of AUC 12.8 day·mg/mL is achieved and maintained with a dose of 200 mg.

The observed nirsevimab serum concentrations in the second season of MEDLEY and MUSIC and the predicted exposure in the second season of MEDLEY and MUSIC are higher than seen in MELODY and MEDLEY season 1, which is reassuring from an efficacy point of view.

There were no events of MA RSV LRTI and hospitalisation in the nirsevimab and palivizumab arms.

Based on the above PK results, the CHMP considered that the efficacy can be extrapolated and thus the beneficial effects observed as regards MA RSV LRTI and hospitalisation can be applied.

3.3. Uncertainties and limitations about favourable effects

There were no events of MA RSV LRTI and hospitalisation, but since the efficacy is based on PK extrapolation this is acceptable.

A rapid decline in nirsevimab serum concentration was observed in 14% (14/96) of the immunocompromised patients from the MUSIC study. It has not been possible to identify risk factors that would allow identification of these patients. It should be noted that in these patients, the mean nirsevimab serum concentrations and the mean exposure were reasonable comparable to the mean exposure seen in the pivotal MELODY study. A warning is added in SmPC section 4.4 on the issue:

"*Immunocompromised children*

In some immunocompromised children with protein-losing conditions, a high clearance of nirsevimab has been observed in clinical trials (see section 5.2), and nirsevimab may not provide the same level of protection in those individuals."

In addition, the CHMP requested the MAH to monitor lack of efficacy data and potential risk factors in patients with protein-losing conditions leading to high clearance of nirsevimab and submit a literature review on this issue in the next PSUR. The MAH will submit a literature review in the next PSUR concerning patients with protein-losing conditions.

A "worst case" scenario where a subject of 1 kg received a 50 mg dose and a subject of 5 kg receive a 100 mg dose late in Season 1 and both receive a 200 mg dose early in Season 2 was simulated and an exposure within the range of the exposure seen in adults were observed, which is considered acceptable. Hence, no minimum time between season 1 and 2 is considered necessary to be included in the SmPC.

3.4. Unfavourable effects

Safety to support the extension of indication to include children up to 24 months of age through their second RSV season, was characterised from addendum data from the MEDLEY Season 2 study (n=262) and from the MUSIC study in immunocompromised children (n=100).

In the MEDLEY Study RSV Season 2, TEAE's by SOC and PT, the distribution across treatment groups were overall comparable. The distribution of the SOC Infections and Infestations was also comparable, though by the PT Upper Respiratory Tract infection, there was a higher percentage (25.0%) in the NIRS/NIRS group compared to PALI/PALI and PALI/NIRS groups where percentages were 1.5% and 17.5% respectively. Numbers were small and no any clinically meaningful trends can be concluded from the imbalances. The pattern of TEAs is generally in accordance with what was observed in RSV Season 1. Treatment-emergent Adverse Events of Grade 3 or Higher Severity by System Organ Class Through at Least 150 Days Post First Dose in Season 2, were numerically higher in the NIRS/NIRS (7.2%) and PALI/NIRS (10.0%) groups compared to the PALI/PALI group (2.4%), mainly driven by the SOC Infections and Infestations. None of these TEAs were considered IP-related. There was only one Grade 4

event reported which was in the NIRS/NIRS group. The incidence of SAEs also was higher in the NIRS/NIRS (9.4%) and PALI/NIRS (10.0%) groups vs the PALI/PALI (0.0%) group for SAEs. Numbers are generally small and no trends of concern can be concluded from the numerical imbalances. The pattern is in accordance with the safety described for RSV Season 1, and no safety concerns are raised. In the MEDLEY Study, Treatment-emergent AEs within 1- and 3-days post first dose in RSV Season 2, were few in the CLD/CHD Cohort, with a maximum of 2.5% (one subject with rhinorrhoea) in the PALI/NIRS treatment group. Treatment-emergent AEs within 7- and 14-days post first dose were generally comparable across treatment groups, though slightly fewer in the subjects receiving IP. No clinically meaningful patterns were disclosed by SOC and PT. No safety concerns are raised. In the MEDLEY study there were numerically more treatment-emergent serious adverse events in the PALI/NIRS group (8 TESAEs in 8 subjects (n=40) and the NIRS/NIRS group (22 TESAEs in 17 subjects (n=180), compared to the PALI/PALI group (0, n=42), most profound in SOC of Infections and infestations. The same pattern was observed in the CLD and CHD subpopulations. Numbers by PT were however small and in accordance with observations in RSV season 1. All treatment emergent TESAEs were considered not related to the IP by the investigator. This is acceptable and no safety concerns are raised.

In the MUSIC Study, RSV Season 1 and 2, 81.0% (n=81/100) subjects experienced at least one TEAE. Of these 23.0% (n=23/100) occurred within 7 days of IP administration. In total, 35% (n=35/100) subjects experienced at least one serious event of Grade 3 severity or higher, however none were considered IP-related. There were three AEs with the outcome of death, that were not considered IP-related either. Five subjects experienced at least one AESI based on investigator assessment, but only one AESI was considered IP-related. Three subjects (3.0%) experienced at least one IP-related skin reaction, and one subject (1%) experienced an IP-related hypersensitivity reaction. Overall, 81% of subjects experienced a TEAE (771 TEAE's in 81 subjects). Not unexpectedly, these predominantly belonged to the SOCs of Infections and Infestations (73.0% (n=73/100)), of which 36% (n=33/100) were upper respiratory tract infection by PT.

Most TEAE's were mild, but 35% (n=35/100) were Grade 3, Most TEAE's were mild, but 35% (n=35/100) were Grade 3, and 7 subjects (7%, n=7/100)) experienced Grade 4 (n=4) and Grade 5 (n=3). TEAE's. In total there were 6 subjects (6%) with 8 mild IP-related TEAEs, of which 4 were pyrexia. None of the Grade 3-5 TEAE's were IP-related. TEAE's reported within 1 day of IP administration occurred in four subjects and were pyrexia (4%), abdominal pain (1%) and rash (1%). Overall, the safety pattern was in accordance with the safety profile for RSV Season 1, and acceptable, bearing in mind that the study cohort in this case, comprised immunocompromised subjects.

With regards to Skin Reactions and Skin Hypersensitivity Reactions in MEDLEY, RSV Season 2, there were a total of 31 (n=262) skin reactions (11.8%) with no apparent imbalances between palivizumab and nirsevimab. In the CHD subpopulation there were a higher percentage of subjects with any skin reaction in the-all nirsevimab group (NIRS/NIRS) than in the-all palivizumab group (PALI/PALI; 25 % vs. 9.1%). There were no reports of IP-related skin reactions (including skin hypersensitivity reactions) in any treatment group. In MUSIC there were a total of 27 treatment-emergent skin reactions in 18 subjects. Only one skin hypersensitivity reaction was considered IP-related, and the subject had no ADA detected post-baseline. It is of note that none of the subjects who developed treatment-emergent ADA responses experienced a skin hypersensitivity reaction. Overall, no concerns for safety regarding hypersensitivity reactions is MEDLEY or MUSIC in RSV Season 2 are evident.

Treatment emergent AESI's were based on the selected MedDRA PTs for immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopaenia. In the MEDLEY study (across RSV Season 1 and 2) there was a higher incidence of hypersensitivity events including anaphylaxis in the NIRS/NIRS group vs. the PALI/PALI group (27.8% vs. 23.8%). In the category of thrombocytopenia there was likewise a slightly higher incidence of thrombocytopenia in the NIRS/NIRS group (3.9% vs. 2.4%). In the CHD subpopulation one subject (NIRS/NIRS) experienced an AESI of heparin-induced

thrombocytopenia, however post baseline ADA was negative. All-over, the incidence of post-baseline ADA was similar between treatment groups (10% vs. 9.6% in the NIRS/NIRS and PALI/PALI treatment group respectively), so no safety concerns are anticipated in this regard. In the MUSIC study there were two events of immune-complex disease, but both were ADA-negative post baseline.

In the MEDLEY study, RSV season 2 there were no AEs with the outcome of death. In the MUSIC study there were three deaths (LRTI not due to RSV, septic shock and tumour haemorrhage) not considered IP related by investigator. No safety concerns are raised with regards to deaths.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 35. *Effects Table for Beyfortus*

Effect	Short description	Unit	Treat-ment	Treat-ment	Control	Uncertainties / Strength of evidence	References
Favourable Effects							
			NIRS/ NIRS	PALI/NIRS	PALI/PALI		
MA RSV LRTI	MA RSV LRTI through 150 days postdose during the second RSV season	Event /N	0/180	0/40	0/42	Unc: Issues regarding blinding in the Nir/nir group.	MEDLEY children with CLD or CHD entering their second RSV season
MA RSV LRTI hospitalisation	MA RSV LRTI hospitalisation through 150 days postdose during the second RSV season	Event /N	0/180	0/40	0/42	Unc: Issues regarding blinding in the Nir/nir group.	MEDLEY children with CLD or CHD entering their second RSV season
			Nirsevimab				
MA RSV LRTI	MA RSV LRTI through 150 days postdose during the second RSV season	Event /N	0			Single arm study. Patients recruited in their first or second season	MUSIC
MA RSV LRTI hospitalisation	MA RSV LRTI hospitalisation through 150 days postdose during the second RSV season	Event /N	0			Single arm study. Patients recruited in their first or second season	MUSIC
Unfavourable Effects							
TEAEs			126/180, 29/40		29/42		MEDLEY

Effect	Short description	Unit	Treat-ment	Treat-ment	Control	Uncertainties / Strength of evidence	References
SAEs			17/180, 4/40		0		RSV season 2
AESIs			24/180, 4/40		4/42		
TEAEs (IP-related)			0		0		
SAE's (IP-related)			0		0		
AESI's (IP-Related)			0		0		
Deaths			0				
TEAEs			80/100				MUSIC
SAEs			28/100				
AESIs			26/100				
TEAEs (IP-related)			7/100				
SAE's (IP-related)			0				
AESI's (IP-Related)	Grade $\leqslant$ 2 juvenile idiopathic arthritis, worsening		2/100				
Deaths			2 (not related)				

Notes Complementing the above, the PK data is hereby enclosed to allow extrapolation.

Table 36: PK data for extrapolation:

Study/Season	N (AUC)	$AUC_{0\text{-}365}$ mg*day/mL	$AUC_{baseline\ CL}$ mg*day/mL	N (Day 151 serum conc)	Day 151 serum conc µg/mL
MELODY (Primary cohort)	954	12.2 (3.5) [3.3-24.9]	21.3 (6.5) [5.2-48.7]	636	26.6 (11.1) [2.1-76.6]
MEDLEY/Season 1	591	12.3 (3.3) [4.1-23.4]	22.6 (6.2) [7-43.8]	457	27.8 (11.1) [2.1-66.2]
MEDLEY/Season 2	189	21.5 (5.5) [7.5-41.9]	23.6 (7.8) [8.2-56.4]	163	55.6 (22.8) [11.2-189.3]
MUSIC/Season 1	46	11.2 (4.3) [1.2-24.6]	16.7 (7.3) [3.1-43.4]	37	25.6 (13.4) [5.1-67.4]
MUSIC/Season 2	50	16 (6.3) [2.2-25.5]	21 (8.4) [5.6-35.5]	42	33.2 (19.3) [0.9-68.5]

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on extrapolation from MELODY, where efficacy was demonstrated in children entering their first RSV season, and on PK data in MEDLEY in vulnerable children entering their second RSV season, the dose

of 200 mg nirsevimab in this population showed similar or higher exposures than seen in MELODY, hence nirsevimab is considered effective in children vulnerable to RSV entering their second RSV season.

Of note, in the MEDLEY study, there were no events of MA LRTI or MA LRTI with hospitalisation through 150 days post first dose in season 2 in any treatment group. The study population has almost completed the full follow-up period, and from day 151 to day 360 only 1 event has occurred, which was in the pal/nir treatment group. In the MUSIC study, no subjects experienced an event during day 0 to day 150 post dose, however, in some of the immunocompromised children a rapid decline in serum nirsevimab was observed, although the exposure was reasonable comparable to the subjects from MELODY study.

In general, the safety profile observed in MEDLEY season 2 and MUSIC is in accordance with the safety observed in season 1 and therefore acceptable.

3.7.2. Balance of benefits and risks

Overall, the provided data from MEDLEY RSV season 2 in patients at higher risk for an RSV infection during their second season, is considered sufficient from an efficacy (extrapolation) and safety point of view.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Beyfortus is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include treatment of children up to 24 months of age who remain vulnerable to severe Respiratory Syncytial Virus (RSV) disease through their second RSV season for BEYFORTUS, based on interim results from studies D5290C00005 and D5290C00008.
Study D5290C00005 (MEDLEY) is a Phase II/III, randomized, double-blind, placebo-controlled study to evaluate the safety of Beyfortus in high-risk children. Study D5290C00008 (MUSIC) is a Phase II, open-label, uncontrolled, single-dose study to evaluate the safety and tolerability, pharmacokinetics, and occurrence of antidrug antibody for Beyfortus in immunocompromised children ≤ 24 Months of Age.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated, together with sections 6.6 (instructions for administration) and 7 (change of MAH). The Package Leaflet is updated

accordingly. Also, Annex II and IIIA (labelling) are amended (administrative change). Version 2.3 of the RMP has been agreed.
In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, and IIIB and to the Risk Management Plan are recommended.

Furthermore, editorial changes were made in Annex II (change in postcode) and IIIA (amended MAH).

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.