14 December 2023
EMA/4418/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Beyfortus

nirsevimab

Procedure no: EMEA/H/C/005304/P46/006

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 19th of July 2023, the MAH submitted a completed paediatric study for Study D5290C00005 (MEDLEY), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The Study was completed by 20 January 2023.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study D5290C00005 (EudraCT no. 2019-000201-69) titled "A Phase 2/3 Randomized, Double-blind, Palivizumab-controlled Study to Evaluate the Safety of MEDI8897, a Monoclonal Antibody with an Extended Half-life Against Respiratory Syncytial Virus, in High-risk Children (MEDLEY)" is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Nirsevimab is a recombinant human immunoglobulin G1 kappa mAb directed against the prefusion conformation of the RSV F protein (Zhu et al 2017).

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

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

Nirsevimab finished product is a sterile, preservative-free, solution for intramuscular injection. It is supplied as a single-dose pre-filled syringe (PFS) in two strengths: 50 mg (in 0.5 mL solution) and 100mg (in 1 mL solution). The formulation is suitable for the paediatric population and the product is already approved for children entering their first RSV season.

2.3. Clinical aspects

Nirsevimab is approved for prevention of RSV disease in all infants (preterm and term), including high-risk infants through their first RSV season and is under review for children up to 24 months of age who remain vulnerable to severe RSV disease through their second season. Nirsevimab (BEYFORTUS®) was first approved in the EU/EEA on 31 October 2022.

2.3.1. Introduction

According to Article 46 of the Regulation of the European Parliament and of the Council (EC) No. 1901/2006, and Regulation 78A (13) and (14) of the Human Medicines Regulations 2012, as inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019, marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within 6 months of completion of the studies concerned.

The MAH submitted a final report for:

- **Study D5290C00005 (MEDLEY)**

A Phase 2/3 randomized, double-blind, palivizumab-controlled study to evaluate the safety of MEDI8897, a monoclonal antibody with an extended half-life against respiratory syncytial virus, in high-risk children (**MEDLEY**)

CHMP's comments

According to the paediatric regulation Article 46, the MAH has submitted the final study report for the MEDLEY study: 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.

Interim data from the study has been evaluated twice by the EMA.

Firstly, at time of initial MAA, where data on the first RSV season in vulnerable children were evaluated.

Secondly, when the population has completed the second RSV season. This part of the study is currently under evaluation by EMA for an indication of prevention of RSV in the children's second RSV season.

In the present submission which includes the final analysis, all CLD/CHD subjects completed follow-up through 360 days post first dose in Season 2 and included all Season 1 and Season 2 safety, efficacy, PK, and ADA data available at the time of the DBL, including Season 1 data through 360 days post first dose.

Please refer to the EPAR of the initial MAA (EMEA/H/C/005304/0000) for detailed description of the MEDLEY study. In this report the results on efficacy and safety up to day 360 in season 2 are assessed, and it is evaluated whether amendment of the SmPC is considered relevant.

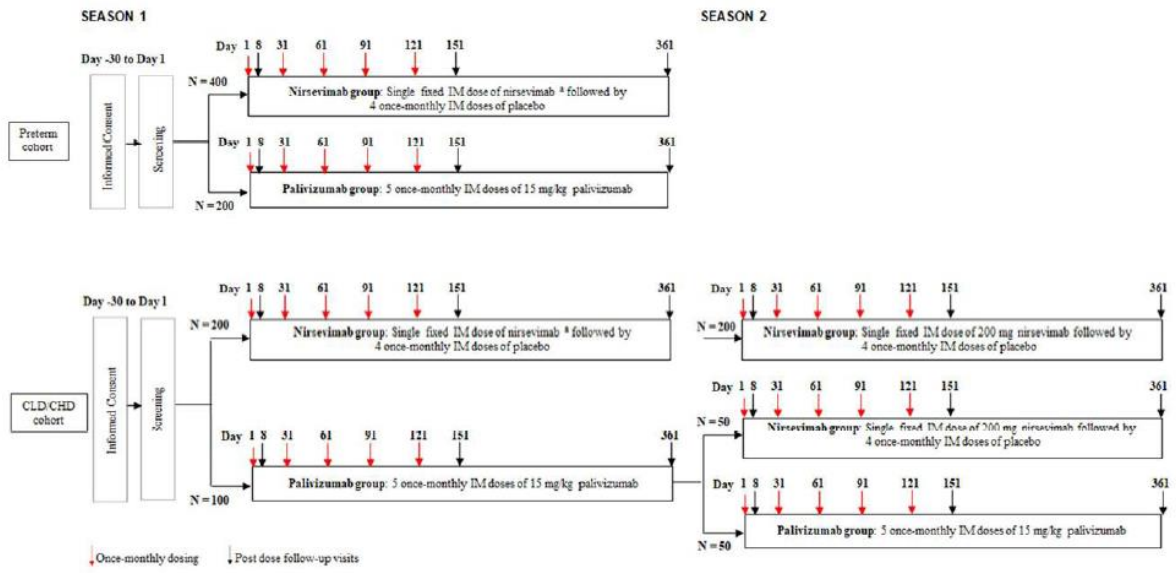
2.3.2. Clinical study

Study D5290C00005 (MEDLEY)

Description

MEDLEY was a pivotal, Phase II/III, multicentre, randomised, double-blind, palivizumab-controlled study in infants at higher risk for RSV severe disease eligible to receive palivizumab when entering their first or second RSV season.

Figure 1 Flow Chart of Study Design



Methods

Study participants

For season 1, the population consisted of two cohorts: preterm infants ≤ 35+0 weeks gestational age with no lower limit of gestational age, besides for the population in Japan in which the gestational age was 29-35 weeks. The second cohort consisted of term and preterm infants in their first year of life with either chronic lung disease of prematurity (CLD) or congenital heart disease (CHD)

For season 2, subjects from the CLD/CHD cohort from the MEDLEY Season 1 study, i.e. patients who had received either nirsevimab or palivizumab were invited to participate.

Children from the preterm cohort from the MEDLEY Season 1 study were not included for the second season intervention.

Treatments

RSV season 1:

In the first RSV season, subjects were randomised to weight-based dose of nirsevimab (50 mg if < 5 kg or 100 mg if ≥ 5 kg) or palivizumab 15mg/kg once monthly x 5. Relevant placebo injections were used in order to keep the blinding.

All subjects were followed through 360 days post dose 1 in RSV Season 1.

RSV season 2:

Subjects in the CLD/CHD cohort dosed with nirsevimab in the first RSV season were assigned to nirsevimab 200 mg IM followed by 4 once-monthly IM doses of placebo (n=200) in the second season. Subjects in the CLD/CHD cohort dosed with palivizumab 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.

Subjects in the CLD/CHD cohort dosed in the second RSV season were followed through 360 days post dose 1 in the second RSV season. Subjects in the CLD/CHD cohort who underwent cardiac surgery with cardiopulmonary bypass received a replacement dose and were followed through 1 year after the replacement dose.

Objective(s) and endpoints:

Primary and secondary objectives and endpoints are shown in the table. The objectives up to day 360 for season 1 and up to day 150 for season 2 was evaluated in a previous procedure. Hence, for the current procedure efficacy data to day 360 for season 2 is evaluated (exploratory endpoint) and safety data up to day 360 for season 2 is evaluated.

Type	Objective	Endpoint	Method of assessment
Primary			
Safety	To evaluate the safety and tolerability of nirsevimab compared to palivizumab when administered to preterm infants entering their first RSV season and children with CLD or CHD entering their first and second RSV season	Safety and tolerability of nirsevimab as assessed by the occurrence of all TEAEs, TESAEs, AESIs, and NOCDs	Appendix 16.1.1, CSP Sections 4.8.3 and 5. Appendix 16.1.9, SAP Section 3.7. SAP Addendum Sections 3.7, 4.1, and 4.2.
Secondary			
PK	To evaluate serum concentrations of nirsevimab and palivizumab	• Nirsevimab and palivizumab serum concentrations • Summary of nirsevimab serum concentrations	Appendix 16.1.1, CSP Section 4.3.3. Appendix 16.1.9, SAP Section 3.9.
ADA	To evaluate ADA responses to nirsevimab and to palivizumab in serum	Incidence of ADA to nirsevimab and palivizumab in serum	Appendix 16.1.1, CSP Section 4.3.4. Appendix 16.1.9, SAP Section 3.8. SAP Addendum Section 4.3.
Efficacy	To assess the descriptive efficacy of nirsevimab when administered as a single IM dose of 50 mg to infants < 5 kg or 100 mg to infants ≥ 5 kg in the first RSV season or a single 200-mg IM dose administered in the second RSV season, in reducing MA LRTI (inpatient and outpatient) and hospitalisation due to RT-PCR-confirmed RSV, compared to palivizumab	• 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	Appendix 16.1.1, CSP Section 4.3.1. Appendix 16.1.9, SAP Section 3.5.

Type	Objective	Endpoint	Method of assessment
Exploratory			
RSV neutralising antibody	To determine anti-RSV neutralising antibody levels in serum afforded by a single dose of nirsevimab compared to 5 monthly doses of palivizumab	• Anti-RSV neutralising 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 $t_{1/2}$)	Appendix 16.1.1, CSP Section 4.3.5.1. Appendix 16.1.9, SAP Section 3.6.3. SAP Addendum Section 3.6.3.
RSV serology	To evaluate exposure to RSV by measuring seroresponses to different RSV proteins in nirsevimab and palivizumab recipients	• Antibody levels to RSV F, Ga, Gb, or N at different time points • Changes in RSV antibody levels (seroresponse) indicating exposure to RSV	Appendix 16.1.1, CSP Section 4.3.5.2. Appendix 16.1.9, SAP Section 3.6.4. SAP Addendum Section 3.6.4.
	To evaluate the levels of maternal RSV-specific antibody in nirsevimab and palivizumab recipients	• 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 $t_{1/2}$)	
HRU and caregiver burden	To assess HRU and caregiver burden for nirsevimab recipients compared to palivizumab recipients	• 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	Appendix 16.1.1, CSP Section 4.3.6 Appendix 16.1.9, SAP Section 3.6.1 and 3.6.2

Type	Objective	Endpoint	Method of assessment
RSV resistance monitoring [a]	To characterise resistance to nirsevimab and palivizumab through genotypic and phenotypic analyses	Genotypic analysis and susceptibility of RSV variants to neutralisation by nirsevimab and palivizumab	Appendix 16.1.9, SAP Section 3.6.5
RSV LRTI after Day 151	To assess the incidence of MA LRTI due to RT-PCR-confirmed RSV, compared to palivizumab after Day 151	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	Appendix 16.1.9, SAP Section 3.6.6

[a] Results for these analyses will be presented in a separate clinical virology study report.

See Table 4 for case definitions of the efficacy endpoints.
ADA = anti-drug antibody; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; Cmax = maximum observed concentration; CSP = clinical study protocol; ER = emergency room; GMFR = geometric mean fold rise; GMT = geometric mean titre; HRU = healthcare resource utilisation; ICU = intensive care unit; IM = intramuscular; LRTI = lower respiratory tract infection; MA = medically attended; NOCD = new onset chronic disease; OTC = over the counter; PK = pharmacokinetics; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; SAP = statistical analysis plan; t1/2 = half-life; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Sample size

The sample size calculation was based on safety, and 600 subjects were to be exposed to nirsevimab and 300 to palivizumab. Hence, approximately 900 palivizumab-eligible infants entering their first RSV season were to be enrolled into one of 2 cohorts: (i) preterm cohort, including approximately 600 preterm infants born < 35 wGA without CLD/CHD, or (ii) 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 and blinding (masking)

The randomization was stratified by age group (≤ 3 months, > 3 to ≤ 6 months, > 6 months) at season 1 and hemisphere within each cohort. Randomization was not stratified by CLD/CHD disease, however, the two cohorts (preterm and CLD/CHD) were balanced between treatment groups.

The study was double-blinded.

Statistical Methods

There were 3 planned analyses for this study:

(i) the Primary Analysis (RSV Season 1 Cohort to Day 151),

(ii) analysis of RSV Season 1 Cohort to Day 361 and RSV Season 2 CHD/CLD Cohort to Day 151

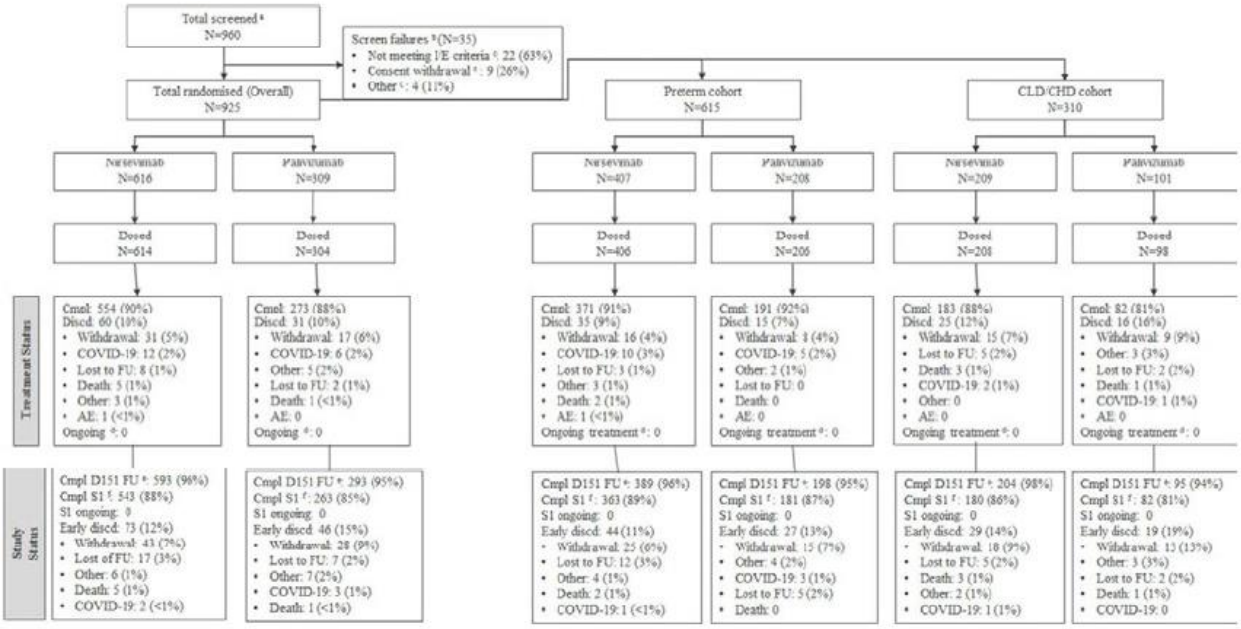
(iii) the Final Analysis (conducted when all subjects completed the last study visit and included all study data collected).

Descriptive statistics were used for efficacy variables. Furthermore, extrapolation was used to assess efficacy, which is currently under evaluation in another procedure (EMEA/H/C/005304/II/0005).

Results

Participant flow

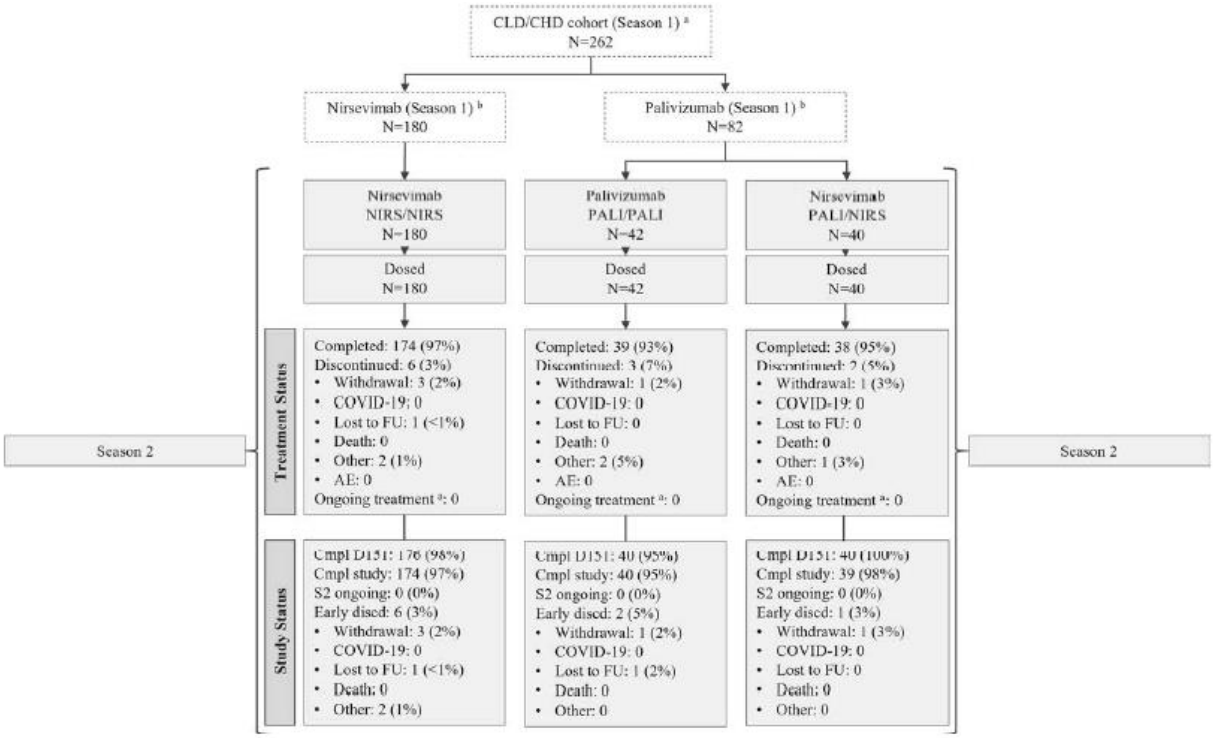
Season 1



[a] Subjects signed the informed consent.
[b] Denominator is the number of subjects screened.
[c] Denominator is the number of screen failures.
[d] Subjects who did not receive Day 121 dose up to the data cut-off date and did not have end of treatment page.
[e] Numerator includes subjects whose study status was ongoing on Season 1 Day 151.
[f] Completed Season 1 = completed Day 361 FU.

AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; Cmpl = completed; COVID-19 = coronavirus disease 2019; D 151 = Day 151; Discd = discontinued; FU = follow-up; I/E = inclusion/exclusion; S1 = Season 1.
Source: Table 14.1.1.1.

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.
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.

Recruitment

Season 1:

In the overall population (CLD/CHD cohort and preterm cohort), 960 subjects were screened, of whom 925 were enrolled (CLD/CHD cohort (n=310) and preterm cohort (n=615)), and randomised (2:1) to nirsevimab (n = 616) or palivizumab (n = 309).

Overall, 99.2% of subjects received IP, 91.1% completed treatment, 95.8% completed Day 151 follow-up for RSV Season 1 and 87.1% completed follow-up for season 1.

Season 2:

Of the 310 subjects in the CLD/CHD cohort, 262 subjects continued into RSV season 2 study. Of those, 180 subjects had been randomised to nirsevimab in season 1, and 82 subjects had been randomised to palivizumab in season 1. The nirsevimab group from season 1 received nirsevimab in season 2 (nirs/nirs, n=180), the palivizumab group were rerandomized to nirsevimab or palivizumab in season 2 (pali/nirs, n=40, pali/pali n=42). Of the 262 subjects who continued into season 2, 256 subjects (97.7%) completed day 151 follow-up and 253 subjects (96.6%) completed the day 360 follow-up.

Baseline data

Season 1:

The baseline characteristics were balanced between the two treatment arms in both cohorts. In the CLD/CHD, the median age at baseline was 1.8 months higher than the preterm group (4.6 months and 2.8 months). As such, the median body weight was also marginally higher (5 kg and 4.3 kg).

Season 2:

At time of dosing in season 2, median body weight was 9.7 kg with IQR of 8.9 kg to 10.9 kg.

PK and immunogenicity results

Following a single dose of nirsevimab, serum concentrations declined linearly over time. In Season 1, there was substantial overlap in serum concentrations between weight groups (< 5 kg, ≥ 5 kg), with comparable serum concentrations in preterm and CLD/CHD subjects. In CLD/CHD subjects, serum concentrations were slightly higher in Season 2, with substantial overlap in the serum concentrations observed for weight-band dose in Season 1 and the fixed dose in Season 2.

Summary of nirsevimab serum concentrations are shown in table 32 and 33.

Table 32 **Summary of Nirsevimab Serum Concentrations (µg/mL) by Weight Group, and Preterm and CLD/CHD Cohort by Scheduled Sampling Time Through 360 Days Post First Dose in Season 1 – As-treated Population (Season 1)**

Group	Summary statistic	Scheduled time					
		Baseline	Day 8	Day 15	Day 31	Day 151	Day 361
Preterm cohort Weight < 5 kg (N = 243)	n	1	13	129	95	176	198
	n < LLOQ	1	0	0	1	1	13
	Arithmetic Mean	NQ	127.38	97.13	82.66	22.71	2.54
	Arithmetic SD	NC	21.97	23.26	23.46	12.57	1.46
	Geometric Mean	NQ	125.64	94.25	75.41	20.38	2.11
	Geometric CV%	NC	17.4	25.6	71.5	55.2	73.2
CLD/CHD cohort Weight < 5 kg (N = 101)	n	0	5	50	46	77	87
	n < LLOQ	0	0	2	0	1	16
	Arithmetic Mean	NA	101.96	96.99	85.44	23.90	2.51
	Arithmetic SD	NA	22.71	39.39	19.20	13.03	2.00
	Geometric Mean	NA	99.71	75.53	83.42	20.97	1.85
	Geometric CV%	NA	24.80	160.40	22.40	67.70	99.4
Preterm cohort Weight ≥ 5 kg (N = 162)	n	0	3	85	65	120	138
	n < LLOQ	0	0	0	1	0	5
	Arithmetic Mean	NA	180.96	142.99	108.83	34.50	4.36
	Arithmetic SD	NA	35.01	27.88	32.99	10.33	3.55
	Geometric Mean	NA	178.51	140.09	96.51	32.79	3.29
	Geometric CV%	NA	20.90	21.10	87.90	34.70	91.50
CLD/CHD cohort Weight ≥ 5 kg (N = 107)	n	0	3	42	56	94	92
	n < LLOQ	0	0	0	1	0	8
	Arithmetic Mean	NA	157.08	130.27	105.46	36.20	4.51
	Arithmetic SD	NA	23.86	48.78	33.12	16.51	6.50
	Geometric Mean	NA	155.80	118.71	93.04	32.30	2.90
	Geometric CV%	NA	16.10	52.10	92.30	55.60	120.7

Subjects < 5 kg received 50 mg, subjects ≥ 5 kg received 100 mg nirsevimab. 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 = 8 in Season 1) and subjects with important protocol deviations of accidentally receiving a second dose of nirsevimab on Season 1 Day 31 were included (n = 4) (see Table 14.1.3.1).
CHD = congenital heart disease; CLD = chronic lung disease; 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; NQ = not quantifiable; SD = standard deviation.
Source: Table 14.5.1.1.1.

Table 33 **Summary of Nirsevimab Serum Concentrations (µg/mL) by Scheduled Sampling Time Through 360 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	169	11	98	108	202	192
n < LLOQ	24	0	3	4	6	16
Arithmetic Mean	3.30	260.11	180.22	153.96	51.24	6.14
Arithmetic SD	2.72	49.23	64.23	71.96	25.01	4.87
Geometric Mean	2.31	256.01	136.98	94.79	39.49	4.28
Geometric CV%	113.1	18.8	193.4	347.3	140.2	123.6

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).

Of the subjects who had serum samples available for testing during Season 1, ADA was detected at any time post-baseline in 5.8% (34/587) of subjects in the nirsevimab group. Treatment-emergent ADA to nirsevimab were detected in 5.7% (22/385) of subjects in the preterm cohort and 5.0% (10/202) in the CLD/CHD cohort.

In the overall population, of all subjects in the nirsevimab group who were post-baseline ADA-positive, a total of 6.3% (2/32) of subjects on Day 361 had neutralising ADA; there were no subjects with neutralising ADA on Day 31 or Day 151.

In the preterm cohort, of all subjects in the nirsevimab group who were post-baseline ADA-positive, a total of 4.3% (1/23) of subjects on Day 361 had neutralising ADA; there were no subjects with neutralising ADA on Day 31 or Day 151.

In the CLD/CHD cohort, of all subjects in the nirsevimab group who were post-baseline ADA-positive, a total of 11.1% (1/9) of subjects Day 361 had neutralising ADA; there were no subjects with neutralising ADA on Day 31 or Day 151.

For those CLD/CHD subjects in the NIRS/NIRS group in Season 2, ADA was detected in 7/174 (4.0%) subjects at Season 1 Day 361. In Season 2, ADA was detected in 1/90 (1.1%), 0/168 (0.0%), and 13/144 (9.0%) subjects at Day 31, Day 151, and Day 361, respectively.

CHMP's comments

The pharmacokinetics are as expected and known from the initial studies and PK linearity was confirmed. The aspired exposures were reached in all subgroups. No changes are required to the SmPC.

The immunogenicity results in RSV season 1 are in line with the ones from the pooled data from the primary cohort of subjects in MELODY and Study 3 entering their first RSV season, who received the proposed dose of nirsevimab regarding post-baseline ADA (5.8 vs. 5.7 %) and treatment-emergent ADA (5.7 vs. 5.6%). Regarding the neutralising antibodies these were higher with 6,3% vs. 0.9% however the absolute numbers were small.

The first dose of nirsevimab did not appear to prime an anti-drug immune response after the second exposure to nirsevimab in Season 2 who received nirsevimab in both seasons, the second dose did

not boost immune responses in previously ADA-positive subjects from Season 1. Of note, in the ongoing type II variation (II-05), the MAH is asked to improve the drug tolerance of the ADA assay.

Efficacy results

The incidence of MA RSV LRTI in Season 2 from 151 through 361 days post first dose by RSV subtype is summarised in Table 34.

There were 2 instances of MA RSV LRTI from 151 through 360 days post first dose in Season 2, in the PALI/NIRS and PALI/PALI groups (1/40 subjects [2.5%] each).

Table 34 Incidence of MA RSV LRTI by RSV Subtype from 151 Through 361 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)
From 151 to 360 days post first dose [a]	1/40 (2.5)	1/40 (2.5)	0/176 (0.0)
RSV A	0/40 (0.0)	1/40 (2.5)	0/176 (0.0)
RSV B	1/40 (2.5)	0/40 (0.0)	0/176 (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.

CHMP's comments

In season 2 from day 151 to 361 post dose, there were only 2 cases of MA RSV LRTI, whereas one of the cases was in the treatment group who had received palivizumab in the first and second RSV season, and the other case was in the treatment group who had received palivizumab in the first season and nirsevimab in the second season. Those descriptive results do not suggest any differences between palivizumab and nirsevimab in the period where the RSV season has ended.

Safety results

Nirsevimab had a favourable and comparable safety and tolerability profile to the current standard of care, palivizumab, in the overall population, preterm infants and those with CLD and/or CHD in Season 1, with similarly favourable and comparable safety and tolerability for subjects with CLD/CHD who received nirsevimab in Season 2.

The types and frequencies of AEs were generally balanced between subjects in the nirsevimab and palivizumab groups, with a low incidence of, investigator-assessed AESIs, NOCDs, and IP-related events (including IP-related skin reactions). There were no subjects with IP-related events of ≥ Grade 3 severity, IP-related SAEs, or IP-related NOCDs.

Overall in RSV Season 1 (up to 360 days post first dose), 72.3% of subjects in the nirsevimab group and 70.7% of subjects in the palivizumab group, had at least one AE. A majority of the events were of Grade 1 or Grade 2 severity. Five fatal events occurred in the nirsevimab group: 2 in the preterm cohort (bronchiolitis and COVID-19) and 3 in the CLD/CHD cohort (cardiac failure congestive, cardiogenic shock, and pneumonia). One fatal event occurred in the palivizumab group: bronchiolitis in an infant in the CLD/CHD cohort. All fatal events were judged as unrelated to IP and these infants all had serious, complex underlying medical conditions at baseline.

The overall frequency of subjects with SAEs was similar between the nirsevimab and palivizumab groups (13.0% vs 12.5%), and none was considered by the investigator to be IP-related. In RSV Season 2 (up to 360 days post first dose in subjects with CHD/CLD), 72.5% of subjects had at least one AE (69.0% in the PALI/PALI group, 77.5% in the PALI/NIRS group, 72.2% in the NIRS/NIRS group); and the majority of events were Grade 1 or 2 severity. No fatal events were reported and the incidence of SAEs and/or AEs ≥ Grade 3 was numerically higher in the NIRS/NIRS (10.6%) and PALI/NIRS (10.0%) groups than in the PALI/PALI (4.8%) group; however, this was not observed within all analysed time points through 30 days post first dose.

None of AEs in RSV Season 2 were considered to be IP-related. Adverse events of special interest based on investigator assessment and NOCDs were reported in one subject each in the NIRS/NIRS group. There were no deaths in Season 2.

CHMP's comments

The final CSR provides additional safety data from MEDLEY Study RSV Season 2, Day 151 to Day 360 post first dose, compared to interim data on TEAE's through at least 150 days post first dose in season 2, currently under evaluation in variation EMEA/H/C/005304/II/0005 for an indication of prevention of RSV in the children's second RSV season.

Patient exposure to IP was 220 subjects in RSV season 2 (MEDLEY, n= 180 + 40 = 220).

Overall, the safety profile of nirsevimab is adequately characterised, and generally in accordance with the safety profile for RSV Season 1. Although, a relatively high proportion of subjects experienced ≥ 1 TEAE in the CLD/CHD subpopulations through up to 360 days post first dose in Season 2, there were no IP-related TEAs of ≥Grade 3, no IP-related serious events, no IP-related AESI based on selected MedDRA PT codes, no IP-related skin reactions and no IP-related NOCD. 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. In the MEDLEY study, RSV season 2 there were no AE's with the outcome of death and there were no reported discontinuations due to adverse events.

No new adverse drug reactions have been reported. Some aspects regarding serious adverse events, safety in special populations and subjects weighing less than 7 kg need to be elucidated, and is currently under review in variation EMEA/H/C/005304/II/0005, with outstanding issues that may lead to amendments of the SmPC.

2.3.3. Discussion on clinical aspects

Regarding the clinical pharmacology PK linearity were confirmed. The submitted study report did not show any new findings and thus did not give rise to changes or amendments in the summary of product characteristics regarding clinical pharmacology.

Regarding clinical efficacy and safety, there is no new information that will lead to an amendment of the SmPC.

In the variation EMEA/H/C/005304/II/0005 which is currently under evaluation by the CHMP, there are still some outstanding issues that may lead to amendments of the SmPC.

3. Rapporteur's CHMP overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.