Final Clinical Study Report Synopsis – Primary Analysis, Safety Analysis, and Final	
Drug Substance	Nirsevimab (MEDI8897)
Study Code	D5290C00004
Edition Number	1.0
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A Phase III Randomised, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Nirsevimab (MEDI8897), a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Late Preterm and Term Infants (MELODY)

Study Dates:

First subject enrolled: 23 July 2019

Last subject last visit: 21 March 2023

The analyses presented in this report are based on:

- a data cut-off date of 11 March 2021 (data lock date of 14 April 2021) for the Primary Analysis complete to Day 361
- a data cut-off date of 09 August 2021 (data lock date of 10 September 2021) for the Primary Analysis complete to Day 511
- a data cut-off date of 31 March 2022 (data lock date of 29 April 2022) for the Safety Analysis complete to Day 151
- a data lock date of 19 April 2023 for the Final Analysis complete to Day 511

Phase of Development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: Not applicable for this Clinical Study Report

Sponsor's Responsible Medical Officer:

[redacted]
AstraZeneca
[redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents. .

2 SYNOPSIS

Study centre(s)

Subjects in the Primary Cohort were dosed at 160 centres in 21 countries.

Subjects in the Safety Cohort were dosed at 130 centres in 29 countries.

Publications

Wilkins D, Yuan Y, Chang Y, Aksyuk AA, Nunez BS, Wahlby-Hamren U et al. Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants. Nat Med. 2023;29:1172–1179.

Muller WJ, Madhi SA, Nunez BS, Cots BM, Bosheva M, Dagan R et al. Nirsevimab for prevention of RSV in term and late-preterm infants. N Engl J Med. 2023;388(16):1533-1534.

Simões EF, Madhi SA, Muller WJ, Atanasova V, Bosheva M, Fernando Cabañas et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. Lancet Child Adolesc Health. 2023;7(3):180-189.

Hammitt LL, Dagan R, Yuan Y, Cots MB, Bosheva M, Madhi SA et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. N Engl J Med. 2022;386(9):837-846.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
• To assess the efficacy of nirsevimab when administered as a single fixed intramuscular dose to term/late preterm infants born ≥ 35 weeks 0 days [a] gestational age and entering their first RSV season, in reducing medically attended LRTI due to RT-PCR confirmed RSV, compared to placebo	• Incidence of MA RSV LRTI (inpatient and outpatient) through 150 days after dosing (ie, during a typical 5-month RSV season)
Secondary Efficacy	
• To assess the efficacy of nirsevimab in reducing hospitalisations due to RT-PCR-confirmed RSV, compared to placebo	• Incidence of MA RSV LRTI with hospitalisation 150 days after dosing (ie, during a typical 5-month RSV season)
Secondary Safety	
• To evaluate the safety and tolerability of nirsevimab when administered as a single fixed intramuscular dose, compared to placebo	• Safety and tolerability of nirsevimab as assessed by the occurrence of TEAEs, TESAEs, AESIs, and NOCDs
Secondary Pharmacokinetics	
• To evaluate single-dose serum concentrations of nirsevimab	• Summary of nirsevimab serum concentrations
Secondary Anti-drug Antibodies	
• To evaluate anti-drug antibodies responses to nirsevimab in serum	• Incidence of anti-drug antibodies to nirsevimab in serum

[a] Subjects in Japan were ≥ 36 weeks 0 days gestational age.

AESI = adverse event of special interest; CSR = clinical study report; LRTI = lower respiratory tract infection; MA = medically attended; NOCD = new onset chronic disease; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Study Design

Study D5290C00004 (MELODY) was a Phase III, multicentre, randomised, double-blind, placebo-controlled, single-dose study to determine if nirsevimab will prevent medically attended respiratory syncytial virus-confirmed lower respiratory tract infection (MA RSV LRTI) in late preterm and term infants born ≥ 35 weeks 0 days GA and entering their first RSV season. All subjects were followed through 510 days after investigational product (IP).

The study was originally designed to analyse the primary endpoint on the full enrolment of approximately 3000 infants. However, the impact of the coronavirus disease 2019 (COVID-19) pandemic on RSV circulation led to a protocol amendment, in consultation with regulatory authorities (Type B meeting, December 2020), to analyse the primary endpoint of

MA RSV LRTI based on the first 1500 subjects enrolled (Primary Cohort). The statistical power for the primary efficacy endpoint was maintained (above 90%); however, the statistical power for the secondary efficacy endpoint, MA RSV LRTI with hospitalisation, was reduced. The study now comprises 2 cohorts: a Primary Cohort (1490 randomised subjects) and a complementary Safety Cohort (1522 randomised subjects). In each cohort, subjects were randomised at a 2:1 ratio to receive a single fixed intramuscular (IM) dose of nirsevimab (50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg) or placebo. Enrolment in the Primary Cohort is complete and included subjects from the Northern Hemisphere (NH) 2019/2020 and Southern Hemisphere (SH) 2020 enrolment seasons (with South Africa being the only SH country). One additional subject was enrolled from Japan in the NH2020/2021 season, prior to pausing the study due to the COVID-19 pandemic. Enrolment in the Safety Cohort is complete and included subjects from the NH2020/2021 and SH2021 enrolment seasons.

The primary objective was met based on the Primary Cohort where the efficacy of nirsevimab against MA RSV LRTI over 150 days in term and late preterm infants was 74.5% (95% confidence interval [CI] 49.6%, 87.1%; $p < 0.0001$) demonstrating both clinical and statistically significant efficacy. Since both the Primary Cohort and Safety Cohort were recruited in the same population of late preterm and term infants under the same protocol and in a fully double-blind manner, efficacy is also presented based on the dataset MELODY (All Subjects). This contains Primary Cohort and Safety Cohort data through 510 days after IP dosing.

For the evaluation of safety, MELODY (All Subjects) included all available safety data from both cohorts through 360 days post dose at the time of database lock (DBL) for the Final Analysis.

Target Population and Sample Size

The study population is healthy late preterm and term infants born ≥ 35 weeks 0 days GA and entering their first RSV season. Subjects with an underlying illness such as cystic fibrosis or Down syndrome with no other risk factors were eligible. Overall, a total of 3012 subjects were randomised in a 2:1 ratio to receive a single IM dose of nirsevimab (N = 2009) or placebo (N = 1003). Randomisation was stratified by hemisphere, NH and SH, and by subject age group at randomisation (ie, ≤ 3.0 months, > 3.0 to ≤ 6.0 months, > 6.0 months). Enrolment of subjects > 6.0 months of age was limited to approximately 500.

A sample size of 3000 was driven by the safety database requirement, and the original study had at least 99% power for the primary efficacy endpoint. More specifically, the sample size of approximately 1500 subjects in the Primary Cohort had at least 99% power to detect a 70% relative risk reduction (RRR), assuming a placebo group MA RSV LRTI incidence of 8%. If

the incidence rate in the placebo group dropped to 4% or higher due to the impact of the COVID-19 pandemic, the sample size still provided at least 90% power to detect a 70% RRR.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

The International Non-proprietary Name of the IP is nirsevimab (formerly MEDI8897).

Nirsevimab was administered as a single IM dose of 50 mg (if < 5 kg weight at time of dosing) or 100 mg (if ≥ 5 kg weight at time of dosing). These infants were not eligible to receive palivizumab, allowing for a placebo comparator group for the determination of efficacy and the safety profile. Batch numbers of nirsevimab used in this study were P65704LA, P65705LA, and P65706LA.

Duration of Treatment

Single dose.

Statistical Methods

There were 3 main planned analyses for this study: the Primary Analysis, Safety Analysis, and Final Analysis. Results of the Primary, Safety, and Final Analyses are reported in this final CSR.

The Primary Analysis was conducted after all randomised subjects from the Primary Cohort (except for one subject enrolled in Japan in the NH2020/2021 season) had been followed through 360 days post dose, and included all efficacy, safety, pharmacokinetic (PK), and anti-drug antibodies (ADA) data collected as of clinical DCO (11 March 2021). Primary and secondary efficacy endpoints were analysed in the Intent-to-treat population 1 analysis set (ITT1), defined as all randomised subjects in the ITT population and from the Primary Cohort. In ITT1, data were analysed according to randomised treatment group.

The Safety Analysis was conducted after all randomised subjects from the Safety Cohort had been followed through at least 150 days post dose. It included all efficacy, PK, ADA, RSV neutralising antibody, RSV serology, and safety data collected on MELODY (All Subjects) as of clinical DCO (31 March 2022).

The Final Analysis was conducted after all randomised subjects had been followed through 510 days post dose. The Final Analysis was performed on the Final Dataset, which included all data collected in the study for the Primary and Safety Cohorts (DBL 19 April 2023).

For the primary analysis of the primary endpoint performed on ITT1, a Poisson regression model with robust variance, including the term of treatment group and randomisation stratification factor (age at randomisation), was used to estimate relative risk (RR) based on the incidence of MA RSV LRTI through 150 days post dose between the nirsevimab and the

placebo groups. During blinded review prior to the database lock for the Primary Analysis, it was revealed that there was no incidence of MA RSV LRTI events through 150 days post dose for SH in the Primary Cohort, which would cause known convergence or estimation issues. Therefore, it was decided to drop the stratification factor hemisphere from the full model and a reduced model (including only the term of treatment group and age at randomisation stratum as covariates) was used instead. Similar consideration also applied to other analyses of the primary efficacy endpoint, where hemisphere was dropped from the corresponding models.

For subjects with multiple MA RSV LRTI events, only the first occurrence was used in the Primary Analysis. The RRR, defined as 1 – RR, and its corresponding 2-sided 95% CI, were estimated from the model. In addition, the 2-sided p-value testing the null hypothesis that the incidence of MA RSV LRTI between the nirsevimab and placebo groups are the same were obtained from the model. The Cochran-Mantel-Haenszel (CMH) test stratified by age group at randomisation was used as the secondary analysis for the primary endpoint. Statistical significance would be achieved if the 2-sided p-value is ≤ 0.05.

For the secondary efficacy endpoint for the Primary Cohort, the incidence of MA RSV LRTI with hospitalisation through 150 days post dose, only the first occurrence was used in the analysis. As the management of more serious RSV disease has been shifting to the outpatient setting, it was recognised that the incidence of RSV hospitalisation in ITT1 may be too low (expected to be approximately 1% in the placebo group) for this secondary efficacy analysis to reach statistical significance ($p \leq 0.05$) within the Primary Cohort alone. Therefore, a prespecified, multiplicity-controlled hierarchical testing strategy was used, based on a pooled analysis consisting of MELODY (Primary Cohort) plus Phase IIb Study D5290C00003 (Study 3) ITT subjects (MELODY [Primary Cohort]/Study 3 Pool) to assess the overall efficacy against MA RSV LRTI with hospitalisation in preterm and term infants. In addition, further analyses assessed the incidence of MA RSV LRTI with hospitalisation in the pooled population of MELODY (Primary Cohort) and Study 3 ITT subjects who weighed < 5 kg (MELODY [Primary Cohort]/Study 3 [Proposed Dose] Pool) and in MELODY (Primary Cohort) alone. A Poisson regression with robust variance, with the term of treatment group, was used to assess MA RSV LRTI with hospitalisation for MELODY (Primary Cohort). For the pooled analysis, in addition to treatment group, the variable study was used as a covariate.

An additional efficacy endpoint for MA RSV LRTI (very severe) was evaluated using a pooled analysis, consisting of MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool, to refine the assessment of MA RSV LRTI with hospitalisation to require oxygen treatment and/or intravenous fluids. A Poisson regression model with robust variance, containing only the term of treatment group was used to estimate the RR on the incidence of observed cases between the nirsevimab and placebo groups. This model deviated from the original planned analyses that included “study” in the model. This was an unintentional error.

For the exploratory evaluation of efficacy in MELODY (All Subjects), Poisson regression models with robust variance, including the term of treatment group and cohort (which identifies the enrolled cohort for each subject) were used to estimate RR based on the incidence of MA RSV LRTI through 150 days post dose, MA RSV LRTI with hospitalisation through 150 days post dose, and MA RSV LRTI (very severe) through 150 days post dose between the nirsevimab and the placebo groups.

Additional exploratory efficacy analyses were also conducted on the Primary Cohort alone to derive respiratory disease incidence (5 case definitions of RSV respiratory disease and 2 additional case definitions of all cause respiratory disease) from 361 through 510 days post dose. This information was collected to evaluate the potential of enhanced disease in the second RSV season in the setting of low serum levels of nirsevimab.

All safety analyses reported in this final CSR at the time of the Final Analysis were conducted on the MELODY (All Subjects) dataset comprising infants from both the Primary Cohort and the Safety Cohort in the as-treated population AT (ie, AT1 and AT2). All safety variables were summarised descriptively by treatment group through 360 days post dose.

Other analyses conducted at the Final Analysis included evaluation of wheezing in the second year of life, anti-RSV neutralising antibody and serology analyses in the AT population, and a summary of all PK data at the time of the Final Analysis.

Study Population

For the Primary Cohort 1626 subjects were screened, with 136 subjects failing screening criteria due to not meeting the inclusion/exclusion criteria (n = 98), lost to follow-up (n = 6), withdrawal of consent (n = 25), or other reason (n = 7). Overall, 1490 subjects were randomly assigned to nirsevimab (n = 994) or placebo (n = 496). Of the 1490 randomised subjects, 987 in the nirsevimab group and 491 in the placebo group were dosed. Twelve subjects (7 randomised to nirsevimab and 5 to placebo) did not receive any IP. The majority of subjects completed the Day 151 follow-up (977 subjects [98.3%] nirsevimab; 488 subjects [98.4%] placebo). A total of 89 subjects (9.0%) randomised to nirsevimab and 43 subjects (8.7%) randomised to placebo completed the study as of clinical DCO (11 March 2021). The majority of early discontinuations in both groups resulted from withdrawal by parent/legal representative (n = 34) and lost to follow-up (n = 12).

For MELODY (All Subjects) 3319 subjects were screened, with 307 subjects failing screening criteria due to not meeting the inclusion/exclusion criteria (n = 192), lost to follow-up (n = 11), withdrawal of consent (n = 90), or other reason (n = 14). Overall, 3012 subjects were randomly assigned to nirsevimab (n = 2009) or placebo (n = 1003). Of the 3012 randomised subjects, 1998 in the nirsevimab group and 996 in the placebo group were dosed. Eighteen subjects (11 randomised to nirsevimab and 7 to placebo) did not receive any IP. The majority

of subjects completed the Day 151 follow-up (1977 subjects [98.4%] nirsevimab; 985 subjects [98.2%] placebo). A total of 1873 subjects (93.2%) randomised to nirsevimab and 923 subjects (92.0%) randomised to placebo completed the study. The majority of early discontinuations in both groups resulted from lost to follow-up (n = 89) and withdrawal by parent/legal representative (n = 79).

Demographic and baseline characteristics were comparable between the nirsevimab and placebo groups. For the Primary Cohort, approximately half of subjects were White (53.5%) or male (51.6%). Median age at randomisation was 2.60 months (range, 0.03 months to 11.10 months), and median weight on Day 1 was 5.50 kg (range, 1.8 kg to 11.5 kg).

For MELODY (All Subjects), approximately half of subjects were White (52.9%) or male (52.3%). Median age at randomisation was 2.53 months (range, 0.00 months to 14.00 months), and median weight on Day 1 was 5.50 kg (range, 1.8 kg to 11.5 kg).

Summary of Efficacy Results

For the primary efficacy endpoint for the Primary Cohort based on the Primary Analysis in ITT1, a single IM dose of nirsevimab demonstrated clinical and statistically significant efficacy with an RRR in the incidence of MA RSV LRTI through 150 days post dose of 74.53% (95% CI: 49.63%, 87.12%) when compared to placebo ($p < 0.0001$; Table S2). Similar results were seen based on the supporting analysis model using stratified CMH test and Poisson regression with robust variance with adjustment for follow-up time. In addition, supplementary analyses for the incidence of MA RSV LRTI using different methods for imputation of MA RSV LRTI status for subjects who did not have a MA RSV LRTI and were not followed through 150 days post dose, demonstrated similar results to that of the Primary Analysis. The sensitivity analyses, to assess the impact of the COVID-19 pandemic on the robustness of the efficacy analyses, confirmed the results of the Primary Analysis.

The results of the exploratory analysis on MA RSV LRTI in MELODY (All Subjects) were consistent with those of the Primary Analysis; a single IM dose of nirsevimab resulted in an RRR in the incidence of MA RSV LRTI through 150 days post dose estimated to be 76.36% (95% CI: 62.27%, 85.18%) when compared to placebo (nominal $p < 0.0001$; Table S2).

Table S2 Incidence of MA RSV LRTI Through 150 Days Post Dose

Analysis	Placebo	Nirsevimab	RRR (95% CI)	p-value
MELODY (Primary Cohort)				
Number of subjects	496	994	NA	
Observed events	25 (5.0%)	12 (1.2%)		
Subjects requiring imputation [a]	6 (1.2%)	15 (1.5%)		
Efficacy [b]			74.53 (49.63, 87.12)	< 0.0001
MELODY (All Subjects)				
Number of subjects	1003	2009	NA	
Observed events	54 (5.4%)	24 (1.2%)		
Subjects requiring imputation [a]	17 (1.7%)	31 (1.5%)		
Efficacy [c]			76.36 (62.27, 85.18)	< 0.0001

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

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

[c] Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including stratification factors [hemisphere and age at randomisation and cohort] as covariates) obtained after missing data imputation.

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; NA = not applicable; RRR = relative risk reduction; RSV = respiratory syncytial virus.

The neutralising activity of nirsevimab against both RSV A and RSV B subtypes was supported by a numerically lower percentage of subjects with primary endpoint events through 150 days post dose in the nirsevimab vs placebo group for both subtypes, in the Primary and Safety Cohorts.

Efficacy against the secondary endpoint, MA RSV LRTI with hospitalisation through 150 days post dose, was analysed according to the hierarchical testing strategy. Efficacy was clinically and statistically significant in the MELODY (Primary Cohort)/Study 3 Pool (RRR vs placebo 73.46% (95% CI 50.16%, 85.87%, $p < 0.0001$) and the MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool (RRR 77.31%, 95% CI 50.26% to 89.65%; $p = 0.0002$; Table S3). However, in Melody (Primary Cohort), the efficacy estimate did not reach statistical significance (RRR vs placebo 62.15%; 95% CI -8.57% to 86.80%; $p = 0.0708$; Table S3).

Similar results were seen based on the supporting analysis model using stratified CMH test and Poisson regression with robust variance with adjustment for follow-up time.

The results of the exploratory analysis on MA RSV LRTI with hospitalisation in MELODY (All Subjects) were consistent with the pooled analysis of MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool, ie, a single IM dose of nirsevimab resulted in an RRR in the incidence of MA RSV LRTI with hospitalisation through 150 days post dose estimated to be

76.84% (95% CI: 49.36%, 89.41%) when compared to placebo (nominal p = 0.0002; Table S3).

Table S3 Incidence of MA RSV LRTI with Hospitalisation Through 150 Days Post Dose

Analysis	Placebo	Nirsevimab	RRR (95% CI)	p-value
MELODY (Primary Cohort)/Study 3 Pool				
Number of subjects	980	1963	NA	
Subjects with observed events	28 (2.9)	14 (0.7)		
Subjects requiring imputation [a]	17 (1.7)	39 (2.0)		
Efficacy [b]			73.46 (50.16, 85.87)	< 0.0001
MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool				
Number of subjects	786	1564	NA	
Subjects with observed events	21 (2.7)	9 (0.6)		
Subjects requiring imputation [a]	10 (1.3)	25 (1.6)		
Efficacy [b]			77.31 (50.26, 89.65)	0.0002
MELODY (Primary Cohort)				
Number of subjects	496	994	NA	
Subjects with observed events	8 (1.6)	6 (0.6)		
Subjects requiring imputation [a]	6 (1.2)	15 (1.5)		
Efficacy [b]			62.15 (-8.57, 86.80)	0.0708
MELODY (All Subjects)				
Number of subjects	1003	2009	NA	
Subjects with observed events	20 (2.0)	9 (0.4)		
Subjects requiring imputation [a]	18 (1.8)	31 (1.5)		
Efficacy [c]			76.84 (49.36, 89.41)	0.0002

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

[b] Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study as covariate for pooled studies) obtained after missing data imputation.

[c] Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study and cohort as covariates) obtained after missing data imputation.

CI = confidence interval; LRTI = lower respiratory tract infection; MA = medically attended; NA = not applicable; RRR = relative risk reduction; RSV = respiratory syncytial virus.

For the efficacy endpoint MA RSV LRTI (very severe), based on the prespecified pooled analysis of MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool, a single IM dose of nirsevimab demonstrated an RRR in the incidence of MA RSV LRTI (very severe) through 150 days post dose of 86.0% (95% CI: 62.5%, 94.8%) when compared to placebo ($p < 0.0001$).

The results of the exploratory analysis on MA RSV LRTI (very severe) in MELODY (All Subjects) were consistent with the pooled analysis of MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool, ie, a single IM dose of nirsevimab resulted in an RRR in the incidence of MA RSV LRTI (very severe) through 150 days post dose estimated to be 78.6% (95% CI: 48.8%, 91.0%) when compared to placebo (nominal p = 0.0005).

Summary of Pharmacokinetic Results

The mean serum concentrations of nirsevimab, administered as a single fixed IM dose (50 mg for infants < 5 kg weight on Day 1, 100 mg for infants ≥ 5 kg weight on Day 1), decreased monoexponentially beyond the Day 31 sampling time point without any evidence of PK nonlinearity. Mean nirsevimab concentrations were similar in infants in the ≥ 5 kg weight group compared with the < 5 kg weight group, with substantial overlap in nirsevimab serum concentrations between the 2 weight groups.

Summary of Pharmacodynamics

Following administration of nirsevimab, RSV neutralising antibody levels (geometric mean concentration) increased > 140-fold from baseline to Day 31 in the nirsevimab group. At Day 151, nirsevimab infants exhibited RSV neutralising antibody levels approximately 50-fold higher than baseline. The RSV neutralising antibody levels decreased between Days 151 and 361 as expected but still remained higher than baseline levels in the nirsevimab group.

The high levels of RSV neutralising antibody in nirsevimab subjects through Day 361 provides further data supporting protection beyond Day 151.

Summary of Immunogenicity Results

Anti-drug antibody was detected post-baseline in 6.5% (127/1945) of subjects in the nirsevimab group and in 1.5% (14/962) of subjects in the placebo group. There was no apparent effect of ADA on PK through Day 151. There was no apparent impact of ADA on nirsevimab safety through Day 361. Due to a limited number of ADA-positive subjects with MA RSV LRTI, the impact of ADA on efficacy could not be evaluated.

Summary of Safety Results

Nirsevimab was well tolerated. Similar types and frequencies of treatment-emergent adverse events (AEs) were reported in both the nirsevimab and placebo groups. Overall, 86.2% of subjects in the nirsevimab group and 84.6% of subjects in the placebo group had at least one AE. The most common AEs (> 10% of subjects in any treatment group) reported with nirsevimab (vs placebo) were upper respiratory tract infection (32.1% vs 31.8%), nasopharyngitis (22.1% vs 23.8%), pyrexia (14.7% vs 12.3%), dermatitis diaper (11.2% vs 10.3%), gastroenteritis (10.7% vs 10.3%), and rhinitis (10.1% vs 10.2%).

The majority of AEs were Grade 1 (60.9% of subjects with nirsevimab vs 56.4% with placebo) or Grade 2 (21.4% of subjects with nirsevimab vs 24.1% with placebo) in severity. Adverse events of ≥ Grade 3 severity were reported in 79 subjects (4.0%) in the nirsevimab group and 41 subjects (4.1%) in the placebo group. The most common Grade 3 AEs reported with nirsevimab compared with placebo were bronchiolitis (0.6% vs 0.9%), RSV bronchiolitis (0.2% vs 0.6%), and pneumonia (0.5% vs 0.1%). Grade 4 or 5 events occurred in ≤ 0.2% of subjects in either group.

There was a similar incidence of AEs considered related to IP by the investigator in the nirsevimab (1.3% of subjects) and placebo groups (1.5% of subjects). Irritability was the most common treatment-related AE reported, occurring in 4 subjects (0.2%) with nirsevimab and 3 subjects (0.3%) with placebo.

The incidence of adverse events of special interest (AESI; defined as immediate [Type I] hypersensitivity [including anaphylaxis], immune complex disease, and thrombocytopaenia) and new onset chronic disease (NOCD) was low in both treatment groups. There were 4 AESIs based on investigator assessment (all in the nirsevimab group) in the study, all were assessed as skin hypersensitivity events and considered related to IP; none of the subjects with these events had ADA detectable post baseline with available assessments. Treatment-emergent NOCDs were reported in 7 subjects (0.4%) in the nirsevimab group and 3 subjects (0.3%) in the placebo group. None of the NOCDs were considered to be treatment-related by the investigator. Treatment-emergent skin reactions considered to be IP-related by the investigator were reported in 12 subjects (0.6%) in the nirsevimab group (onset ≤ 1 to ≤ 14 days post dose) and 3 subjects (0.3%) in the placebo group (onset ≤ 3 to ≤ 14 days post dose).

There was no apparent impact of ADA on safety through Day 361.

Four deaths, all in the nirsevimab group, were reported through 360 days post dose: 2 due to gastroenteritis; one due to skull base fracture; and one due to unknown cause occurring on Day 140 following dosing with 50 mg nirsevimab on Day 1, an autopsy was not performed and the death remains unexplained. None of the deaths were considered related to IP by the investigator. The causes of death were attributed to common causes of infant mortality in the region where the infant was enrolled or due to underlying medical conditions. There were two non-treatment emergent deaths. One death (due to a road traffic accident) occurred in the nirsevimab group after the Day 361 reporting period, on Day 440, and one death (late neonatal sepsis) occurred in a subject who was randomised but never dosed.

The proportion of subjects with at least one serious adverse event (SAE) was similar between the nirsevimab and placebo groups (7.5% vs 8.3%). Serious and/or ≥ Grade 3 severity AEs were reported in 161 subjects (8.1%) in the nirsevimab group and 85 subjects (8.5%) in the placebo group. The most common (> 0.5% of subjects in either treatment group) SAEs in the

nirsevimab group compared with the placebo group were bronchiolitis (1.4% vs 1.7%), gastroenteritis (0.7% vs 0.5%), pneumonia (0.5% vs 0.7%), and respiratory syncytial virus bronchiolitis (0.3% vs 1.0%). One SAE in the placebo group (fever neonatal) was considered treatment-related by the investigator.

Conclusions

- In term and late preterm infants ≥ 35 wGA (MELODY [Primary Cohort]), nirsevimab demonstrated clinical and statistically significant efficacy (RRR 74.5%; 95% CI 49.6%, 87.1%; $p < 0.0001$) against the primary endpoint MA RSV LRTI. A consistent result was found in an exploratory analysis in MELODY (All Subjects) with efficacy against MA RSV LRTI (RRR 76.4%; 95% CI 62.3%, 85.2%) similar to that demonstrated in MELODY (Primary Cohort).
- Pooled analyses (multiplicity-controlled) were prespecified to estimate the efficacy of nirsevimab in subjects who received the proposed dose across the target population of term and preterm infants ≥ 29 wGA entering their first RSV season. In the MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool, nirsevimab demonstrated efficacy against MA RSV LRTI with hospitalisation (RRR 77.3%; 95% CI 50.3%, 89.7%; $p = 0.0002$).
- For the secondary endpoint MA RSV LRTI with hospitalisation, a non-statistically significant result was seen (RRR 62.1%; 95% CI -8.6% to 86.8%; $p = 0.0708$) in MELODY (Primary Cohort) alone.
- When the efficacy analysis of MA RSV LRTI with hospitalisation was repeated in the larger MELODY (All Subjects) dataset (exploratory analysis), an RRR of 76.8% (95% CI: 49.4 to 89.4) was observed.
- Efficacy against the exploratory endpoint MA RSV LRTI (very severe) was estimated to be 64.2% (95% CI -12.1 to 88.6) in MELODY (Primary Cohort) and 78.6% (95% CI 48.8 to 91.0) in MELODY (All Subjects).
- Impact analysis demonstrated that for 1000 infants immunised, the number of cases of LRTI due to any cause averted with nirsevimab was estimated to be 93.6 (95% CI 63.0, 124.0) and the number of hospitalisations for respiratory illness due to any cause averted was estimated to be 17.7 (95% CI 2.0, 33.0).
- Nirsevimab serum concentrations declined in a linear fashion after 31 days post dose in subjects < 5 kg at Day 1 and subjects ≥ 5 kg at Day 1, with a substantial overlap in nirsevimab serum concentrations between weight groups.
- The safety analyses from MELODY (All Subjects) showed that incidences of AEs were generally comparable between the nirsevimab and placebo groups. The frequency of AEs ≥ Grade 3 severity, SAEs, AESIs and treatment-related AESIs, and treatment-related skin reactions were low and similar between treatment groups.
- AESIs were reported in 4 subjects (0.2%) in the nirsevimab group (PT rash maculo-papular [2 subjects], PT rash [1 subject], PT rash papular [1 subject]). These were all assessed as skin hypersensitivity events and considered related to IP by the investigator. Three of these events were of Grade 1 severity and one was of Grade 3 severity.

- Treatment-emergent NOCDs were reported in 7 subjects (0.4%) in the nirsevimab group and 3 subjects (0.3%) in the placebo group. None of the NOCDs were considered to be related to IP by the investigator.
- No deaths or SAEs were considered by the investigator to be related to nirsevimab. Four deaths occurred through 360 days post dose in the nirsevimab group (none in the placebo group).
- The incidence of ADA was low, and in subjects who were post-baseline ADA positive, there was no apparent effect of ADA on PK through Day 151. There was no apparent impact of ADA on nirsevimab safety through Day 361. Due to a limited number of ADA-positive subjects with MA RSV LRTI, the impact of ADA on efficacy could not be evaluated.
- A single IM dose of nirsevimab offers the potential to address the large unmet medical need of preventing RSV lower respiratory tract disease in infants from birth entering their first RSV season.