Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Delegate's overview

Active ingredient(s): nirsevimab

Proprietary product name: BEYFORTUS

Sponsor: Sanofi-Aventis Australia Pty Ltd

Submission number: PM-2022-04428-1-2

eID e006590

06 September 2023

TGA Health Safety Regulation

Submission information

Submission number	PM-2022-04428-1-2
Active ingredient(s)	nirsevimab
Product name	BEYFORTUS
Strengths/dose form	BEYFORTUS 50 mg solution for injection in prefilled syringe BEYFORTUS 100 mg solution for injection in prefilled syringe
Sponsor	Sanofi-Aventis Australia Pty Ltd (There was a change of sponsorship from AstraZeneca Pty Ltd during the evaluation)
Description of the submission/proposed indication	The Sponsor proposes to register a new therapeutic entity with the following indication: BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: (i) Neonates and infants entering or 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, which may include but is not limited to children with: - Chronic lung disease of prematurity (CLD) - Haemodynamically significant congenital heart disease (CHD) - Immunocompromised states - Down syndrome - Cystic fibrosis - Neuromuscular disease - Congenital airway anomalies. BEYFORTUS should be used in accordance with available official recommendations. <u>Dosing recommendations</u> *Infants entering their first RSV season* The recommended dose is a single fixed dose of 50 mg for infants with body weight <5 Kg and a single fixed dose of 100 mg for infants with body weight ≥5 Kg. BEYFORTUS should be administered from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season.

	Children who remain vulnerable to severe RSV disease entering their second RSV season The recommended dose is a single dose of 200 mg given as two intramuscular (IM) injections (2 x 100 mg). For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of BEYFORTUS, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.
Summary of data	The clinical data package for this submission included three pivotal, double-blind, randomised studies (Study 3 [D5290C00003], MELODY [D5290C00004] and MEDLEY [D5290C00005]) and an open-label study in immunocompromised infants/children (MUSIC [D5290C00008]). In addition, there were two completed dose-escalation, safety, PK and anti-drug antibody studies (Study 1 [D5290C00001] and Study 2 [D5290C00002]), which (along with MELODY, Study 3, and MEDLEY) contributed data for population PK modelling. The submitted data are sufficient to recommend approval. Areas of uncertainty include the low number of subjects in the MEDLEY and MUSIC studies and the extrapolation of efficacy to high-risk subgroups.
Preliminary view	While a decision is yet to be made, at this stage I am inclined to approve the registration of the product. The final wording of the indication will be confirmed following ACM advice. If registration was approved, I would propose the following additional conditions of registration: Quality and RMP conditions of registration
Outstanding issues	See questions below for the Sponsor and the ACM.

Questions for the sponsor

1. For vulnerable children up to 24 months of age, is there a minimum time frame between receiving the first and second dose of BEYFORTUS? If data are available, please include this in Section 4.2 of the product information.

2. Could the Sponsor please provide clarification regarding the dosing in children up to 24 months of age? For premature infants, will this be according to corrected age or chronological age? How will this information be communicated to health care professionals?

Request for ACM advice

ACM meeting number: 41 **Date (of meeting): 5-6 October 2023**

Summary of issue/s for advice	
Advice sought	1. Please comment on the findings of the MEDLEY study, in light of the proposed indication and dosing for children entering their second season of RSV and the low number of subjects in this study. 2. Related to point 1, does the ACM agree with extrapolation of efficacy to each of the high-risk groups included in the proposed indication, based on the inclusion criteria and results of the MEDLEY and MUSIC studies? What is the view of the ACM regarding the alternative wording of the indication proposed by the Delegate? 3. Does the ACM have concerns with using BEYFORTUS routinely in all infants during their first RSV season? 4. Related to point 3, in what settings does the ACM anticipate that BEYFORTUS will be administered to infants? Will this occur in hospital clinics, local immunisation clinics and general practices? 5. The ACM is also requested to provide advice on any other issues that it thinks may be relevant.

s22 [redacted]

Delegate of the Secretary under regulation 35A of the Therapeutic Goods Regulations 1990

06 SEP 2023

Date

Body of overview

Background

Condition

RSV is the most common cause of lower respiratory tract infection among infants and young children globally and is the major cause of hospital admission, with an estimated 33 million clinical cases (uncertainty range [UR] 25·4–44·6 million), 3.6 million (2·9–4·6 million) hospitalisations in children <5 years of age and 26 300 (15 100–49 100) RSV-associated acute lower respiratory infection in-hospital deaths in 2019.[1] In infants aged 0-6 months, the burden is greater, with an estimated 6·6 million RSV-associated acute lower respiratory infection episodes (4·6–9·7 million).[1]

While the mortality rate due to RSV infection is low in high-income countries, inpatient disease burden is high, with the greatest burden occurring in young infants.

It has been estimated that, in the absence of immunisation, there are approximately 590000 medically attended RSV LRTIs annually among US infants.[2]

In Australia, RSV was made a nationally notifiable disease in July 2021. A community-based, birth cohort from Brisbane followed children until their second birthday and demonstrated that RSV incidence in the first 2 years of life was 0.46 (95% CI = 0.37–0.58) episodes per child-year. Of 82 episodes linked with symptom data, 60 (73.2%) were symptomatic, 28 (34.1%) received community-based medical care, and 2 (2.4%) led to hospitalisation.[3]

Infants with serious underlying comorbidities remain vulnerable for severe RSV disease beyond their first RSV season. These include infants with prematurity, chronic lung disease, congenital heart disease, cystic fibrosis, neuromuscular conditions, Down syndrome, or immunocompromised states.

(Sponsor cover letter, 28 October 2022)

Current treatment options

Palivizumab, a humanised IgG1 monoclonal antibody, is currently approved by the TGA for the following indications: (see SYNAGIS PI and Sponsor cover letter)

Synagis (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (gestational age less than or equal to 35 weeks at birth) and children with haemodynamically significant congenital heart disease (CHD). (See Section 5.1 Pharmacodynamic properties-Clinical Trials).

[1] Li Y et al, Lancet 2022; 399: 2047–64
[2] Rainisch G et al, Vaccine 2020; 38(2): 251–257
[3] Takashima et al, European Journal of Pediatrics 2021,180:2125–2135

The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community.

Delegate comment: Palivizumab is not funded by the PBS. It is provided at the discretion of individual hospitals. It is funded by the Western Australian Department of Health for infants and young children for certain categories. (Sponsor cover letter, 28 October 2022)

Australian regulatory status

Nirsevimab is a new biological entity and is not yet registered in Australia.

International regulatory status

As per the response to the Section 31 request, the submission was approved by Health Canada in April 2023, the European Union in October 2022, and Great Britain in November 2022. The submission was recently approved in the USA in July 2023.

The application is under review in Japan and Switzerland and has not yet been submitted in New Zealand or Singapore.

The Sponsor clarified in Module 1.11.3, Data similarities and differences (Response to the Section 31 request) that there are essentially three global data packages for nirsevimab:

1. Initial new product data package based on the Season 1 clinical data, initially submitted in the EU and Great Britain.
2. Season 2 data package containing Season 2 clinical data only – submitted in the EU after approval of the initial new product/Season 1 clinical data package. Additional quality updates have been managed via other post approval variations.
3. Revised new product data package updated with Season 2 clinical data and other documentation where relevant – submitted in most other markets including Australia, Canada, USA and other major markets.

At the request of the Delegate, the Sponsor provided an update of the international regulatory status. A response was received by the TGA on 10 August 2023:

The Season 2 data was submitted in the EU in April 2023. Approval is expected November 2023. The variation will be submitted in Great Britain via the European Commission Decision reliance procedure once approved in the EU.

The following table outlines the approved indications for the FDA, EMA and Health Canada and the proposed indication for Australia.

TGA (proposed)	FDA	EMA	Health Canada
BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: i) Neonates and infants entering or during their first RSV season. ii) Children up to 24 months of age who remain vulnerable to	BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: -Neonates and infants born during or entering their first RSV season.	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.	BEYFORTUS (nirsevimab injection) 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

severe RSV disease through their second RSV season, which may include but is not limited to children with: - Chronic lung disease of prematurity (CLD) - Haemodynamically significant congenital heart disease (CHD) -Immunocompromised states - Down syndrome - Cystic fibrosis - Neuromuscular disease - Congenital airway anomalies BEYFORTUS should be used in accordance with available official recommendations.	-Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.		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 (CLD) -Hemodynamically significant congenital heart disease (CHD) -Immunocompromised states -Down syndrome - Cystic fibrosis -Neuromuscular disease -Congenital airway anomalies.

Manufacturing and quality control (Module 3) data evaluation

There were no objections on quality grounds to the approval of BEYFORTUS. Please refer to the Quality (Module 3) Summary, included as an attachment for the ACM.

Several GMP clearances from the previous Sponsor, AstraZeneca, were still pending approval and/or renewal. In line with the Sponsor change from AstraZeneca Pty Ltd to Sanofi-Aventis Australia Pty Ltd, the Sponsor has been requested to ensure all GMP clearances refer to the new Sponsor. The Sponsor has been notified that all GMP clearances must be valid before Module 3 can recommend approval of the application.

Structure and manufacture

Nirsevimab is a is a human IgG1κ monoclonal antibody with a YTE mutation in the Fc domain. The Fab domains of nirsevimab bind specifically to the pre-fusion conformation of the respiratory syncytial virus (RSV) fusion (F) protein to prevent the infection of human cells by RSV. The molecular weight is approximately 150kDa comprising two heavy chain molecules and two light chain molecules.

The active ingredient was produced using recombinant DNA technology.

Delegate note: Nirsevimab has been engineered with a triple amino acid substitution (M252Y/S254T/T256E [YTE]) in the fragment crystallisable (Fc) region to prolong serum half-life.

Formulation and Manufacture

The Module 3 evaluator noted that the final formulation intended for marketing was used in the phase 3 clinical trials. All excipients are well known pharmaceutical ingredients and their quality is compliant with European, US and Japanese pharmacopoeial standards.

Storage and shelf life

The recommended Drug Product storage condition is 18 months when stored at 2-8°C, protected from light. According to the PI, 'BEYFORTUS may be kept at room temperature (Store below 25°C) for a maximum of 8 hours. After removal from the refrigerator, BEYFORTUS must be used within 8 hours or discarded. Keep the prefilled syringe in the outer carton in order to protect from light. Do not shake or expose to heat.'

Quality – related proposed conditions of registration

For a complete description of the quality-related conditions of registration, please refer to the Quality (Module 3) product summary.

Laboratory Testing & Compliance with Certified Product Details (CPD)

i. All batches of BEYFORTUS supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

ii. When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results https://www.tga.gov.au/resources/lab-test-reports and periodically in testing reports on the TGA website.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Non-clinical (Module 4) data evaluation

There were no non-clinical objections to registration. Please refer to the non-clinical evaluation report, included as an attachment for ACM.

The non-clinical evaluator highlighted that the submitted Module 4 dossier was in accordance with relevant ICH guideline for non-clinical assessment of biological medicines (ICH S6[R1]). The overall quality of the non-clinical dossier was good. The pivotal safety-related studies were GLP compliant.

Pharmacology studies suggested efficacy against RSV A and B.

Nirsevimab was well tolerated in monkeys.

No off-target sites were identified in a panel of human tissues (including a range of juvenile, neonate and fetal tissues).

In vitro studies revealed variants with mutations at positions 68, 201 and 208 in the RSV binding site are resistant to nirsevimab. While naturally occurring mutations at these sites have not been observed in a clinical setting, viral resistance will need to be monitored clinically. Amino acid modification in nirsevimab development did not have any effect on effector function. It was concluded that the potential risk of treatment failure due to the development of viral variants that are resistant to nirsevimab would need to be monitored clinically.

The non-clinical evaluator recommended changes to the product information, most of which have been accepted by the Sponsor. Following Milestone 5, the non-clinical evaluator proposed

a pregnancy category recommendation of B2. The Delegate recommends the PI be updated accordingly. (see Appendix 1, Review of Product Information)

Clinical (Module 5) data evaluation

The clinical data package for this submission includes three pivotal, double-blind, randomised studies (Study 3 [D5290C00003], MELODY [D5290C00004] and MEDLEY [D5290C00005]) and an open-label study in immunocompromised infants/children (MUSIC [D5290C00008]).

In addition, there were two completed dose-escalation, safety, PK and ADA studies (Study 1 [D5290C00001] and Study 2 [D5290C00002]), which (along with MELODY, Study 3, and MEDLEY) contributed data for population PK modelling. Australian sites participated in Study 3 and MELODY.

Delegate comment

Final clinical study reports for Study D5290C00004 (MELODY), Study D5290C00005 (MEDLEY), and Study D5290C00008 (MUSIC) were provided with the Milestone 5 response. Where relevant, results from the final clinical study results have been included in the summary of each study described in the Overview.

Study D5290C00003 was completed by the time of initial submission.

Published papers for Study 3, Study D5290C00004 (MELODY) Study D5290C00005 (MEDLEY), and the pooled analysis for Study 3 and MELODY are included in the attachments for the ACM.

Pharmacology

The two completed dose-escalation, safety, PK and ADA studies Study 1 [D5290C00001] and Study 2 [D5290C00002]) are described in section 19.1 of the CER and will not be discussed in detail in this Overview.

An overview of the studies is summarised below.

Overview of phase 1 studies

Study, dates, location	Design	Population	Number of subjects dosed	Follow up
Single centre in the USA, Apr 2014 to Jun 2015	Phase 1, first-time-in-human, randomised, double-blind, placebo-controlled, dose-escalation study	Healthy males/females aged ≥18 to <50 years	136	361 days post dose
Ten sites in the USA, Chile, and South Africa, Jan 2015 to Sep 2016	Phase 1b/2a, randomised, double-blind, placebo-controlled study	Healthy preterm infants born between 32 weeks 0 days and 34 weeks 6 days gestational age who entered their first RSV season.	89	361 days post dose

Pharmacokinetics (PK)

Absorption

Following IM administration, the median (range) time to maximum concentration was 6 (1 to 28) days. The estimated absorption $t_{1/2}$ was 1.7 days, and the estimated absolute bioavailability was 84%.

Distribution

Volume of distribution – derived from PopPK:

The estimated central and peripheral volumes of distribution of nirsevimab were 216 mL and 261 mL, respectively, for a typical 5 kg infant aged 11.1 months.

Metabolism

Nirsevimab, as a human monoclonal antibody is degraded by proteolytic enzymes widely distributed in the body. Nirsevimab is not metabolised by hepatic enzymes.

No clinical studies were conducted to investigate the effect of renal or hepatic impairment on nirsevimab. Monoclonal antibodies are not primarily cleared via the renal or hepatic pathway and change in these functions are therefore not expected to influence nirsevimab clearance.

Excretion

As a typical mAb, nirsevimab is eliminated by intracellular catabolism with no evidence of target-mediated systemic clearance (note: the target of nirsevimab is exogenous). The estimated clearance for nirsevimab was 3.42 mL/day for a typical 5 kg infant with a postmenstrual age of 11.1 months. The predicted mean (SD) terminal elimination half-life in infants was 71.4 (11.4) days.

Pharmacokinetics according to age

Nirsevimab has been studied in adults and preterm and term infants. An effect of postmenstrual age was estimated in the popPK analysis. There is a high correlation between age and body weight in children.

Pharmacokinetics in the target population

The PK of nirsevimab in healthy preterm infants born ≥32 to <35 weeks GA was evaluated in Study 2 (Section 19.1.1 of the CER). Exposure increased in a less than dose-proportional manner from 10 mg to 25 mg and approximately dose-proportionally from 25 mg to 50 mg. The mean terminal t½ in serum ranged from 62.5 to 72.9 days across IM doses.

Drug-drug interactions

The EU public assessment report provided commentary on this, noting that due to the nature of the product, drug-drug interactions are not expected and it is acceptable that no drug-drug interaction studies have been conducted. Interaction/ interference with the immune response for concomitantly administered routine paediatric vaccines is unlikely. It was noted that routine vaccines were given in the safety pool.[4]

Population PK data (popPK)

The Population PK Modeling of Nirsevimab in Term and PreTerm Children, and Extrapolation to Higher Risk Children (30 August, 2022) report was evaluated for robustness of methodology, consistency with regulatory guidelines and validity of results.

The purpose of the analysis was to support the dosing strategy of nirsevimab and the extrapolation of efficacy to the high-risk population based on PK data. The proposed dosing

[4] Assessment report, BEYFORTUS, 15 September 2022 EMA/786523/2022.
https://www.ema.europa.eu/en/documents/assessment-report/beyfortus-epar-public-assessment-report_en.pdf

strategy was 50 mg for infants < 5 kg in Season 1, 100 mg for infants ≥ 5 kg in Season 1 and 200 mg in Season 2.

Please refer to the Population PK results for further details. The pharmacometrics evaluator noted that nirsevimab CL in Season 2 appeared to be lower than that in Season 1 resulting in higher observed serum concentrations. The reason for this was not clear. Possible explanations proposed were difference in the relationship between body weight and CL in the second year of life compared to the first year, an effect of CHD/CLD or delivery of the 200 mg dose in Season 2 as two injections, each 100 mg.

The model adequately predicted nirsevimab concentrations in immunocompromised children children, suggesting comparable exposures in this population.

Extrapolation criteria for efficacy on the basis that similar nirsevimab exposures are expected to produce similar response were considered to be justified. As >90% of exposures in MEDLEY Season 2 were above the exposure threshold for efficacy, the criteria for extrapolation of efficacy in MEDLEY Season 2 were successfully met. In addition, distributions of Day 151 concentrations and $AUC_{0\text{-}365}$ in MEDLEY Season 1 were comparable to those in MELODY (also Season 1) and were higher in MEDLEY Season 2 than those in MELODY (Season 1), confirming adequate exposures for efficacy in these populations.

The pharmacometrics evaluator concluded that the population PK model development and qualification methodology was sound and the predictive performance of the model was adequate to predict exposures across paediatric subgroups.

Assuming no safety risk at exposures for the 3000 mg IV dose in adults, the findings support the conclusion that the proposed dosing schedule (50 mg for < 5 kg infants and 100 mg for ≥ 5 kg infants in Season 1 and 200 mg dose in Season 2) is expected to result in safe and efficacious exposures.

Delegate comment: the Sponsor notified the TGA in their Section 31 Response of an erratum in the Pop PK model which has since been addressed by the pharmacometrics evaluator and clinical evaluator.

Pharmacodynamics (PD)

The evaluator concluded that following administration of a single dose of nirsevimab in infants entering their first RSV season in Study 2 and 3, MELODY (Primary Cohort), and MEDLEY Season 1, dose dependent high increases in serum anti-RSV neutralising antibody levels were demonstrated. The fold increase in neutralising antibodies was far greater than those seen induced by RSV infection itself. Durability of these high 'protective' levels was demonstrated and would provide protective levels for the average 5-month RSV season, supporting single dose in Season 1 of RSV. Boosting levels in RSV season 2 in those who are highly vulnerable was deemed to be safe. Serum anti-RSV neutralising antibody levels were correlated with nirsevimab serum concentrations across all dose levels, confirming anti-RSV-neutralising activity of nirsevimab. (CER Section 5.2)

Efficacy

Overview of Phase 2 and 3 studies

Phase 2				
Study, dates, location	**Design**	**Population**	**Number of subjects randomised**	**Follow up**
D5290C00003 03 November 2016 to 06 December 2018 164 centres, including Northern and Southern hemispheres	Phase 2b, randomised, double-blind, placebo-controlled, single-dose	Healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age	1453 Placebo: 484, MEDI8897: 969	361 days post dose
MUSIC [D5290C00008] 19 August 2020 to 17 February 2023. 28 sites, Northern and Southern hemispheres	Phase 2, open-label, uncontrolled, single-dose study	Immunocompromised children ≤24 months of age at the time of dose administration.	100 enrolled and dosed	361 days post dose
Phase 3				
MELODY [D5290C00004] 23 July 2019 to 21 March 2023 Primary Cohort: 160 centres Safety cohort: 130 centres Enrolment included Northern and Southern hemispheres	Phase 3, multicentre, randomised, double-blind, placebo-controlled, single-dose study	Late preterm and term infants born ≥35 weeks 0 days GA and entering their first RSV season	3012 Placebo: 1003 Nirsevimab: 2009	510 days post dose
MEDLEY [D5290C00005] 30 July 2019 to 20 January 2023 Subjects in Season 1 were dosed at 126	Phase 2/3 randomised, double-blind, palivizumab-controlled study	High-risk infants eligible to receive palivizumab when entering their first or second RSV season: preterm (≤ 35 weeks gestational age) and CLD/CHD cohorts)	925 616 nirsevimab, 309 palivizumab (615: preterm cohort, 310: CLD/CHD cohort)	360 days post first dose in season 2

centres in 25 countries. Subjects in Season 2 were dosed at 58 centres in 18 countries. Enrolment included Northern and Southern hemispheres*				

*Enrolment paused in Southern Hemisphere in March 2020

Study D5290C00003 (Study 3)[5]

Study D5290C00003 (Study 3) was a Phase 2b, randomised, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 (nirsevimab) would be efficacious in reducing medically attended RSV-confirmed LRTI in healthy preterm infants entering their first RSV season. The population to be enrolled was healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days gestational age who would not receive RSV prophylaxis based on the American Academy of Pediatrics or other local or national guidelines.

Objectives and Endpoints

Objectives	**Endpoints**
Primary efficacy	
Assessed the efficacy of MEDI8897 when administered as a single 50 mg IM dose to healthy preterm infants born between 29 weeks 0 days and 34 weeks 6 days GA and entering their first RSV season for the reduction of medically attended LRTI due to RT-PCR-confirmed RSV, compared to placebo	Incidence of medically attended LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season.
Secondary efficacy	
Assessed the efficacy of MEDI8897 for the reduction of hospitalisations due to RT-PCR-confirmed RSV, compared to placebo	Incidence of hospitalisations due to RT-PCR-confirmed RSV over the duration of the 5-month RSV season
Secondary safety	
Evaluated the safety and tolerability of MEDI8897 when administered as a single fixed IM dose, compared to placebo.	Safety and tolerability of MEDI8897 as assessed by the occurrence of all TEAEs, TESAEs, AESIs, and NOCDs
Secondary pharmacokinetics	

[5] Griffin MP et al, N Engl J Med 2020;383:415-25.

Evaluated single-dose serum concentrations of MEDI8897	Single-dose MEDI8897 serum concentrations
Secondary anti-drug antibodies	
Evaluated ADA responses to MEDI8897 in serum	Incidence of ADA to MEDI8897 in serum

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, MEDI8897= nirsevimab

Exploratory objectives and associated endpoints are described in the CER and Clinical study report and included assessment of healthcare resource utilisation and caregiver burden.

Study design

Subjects were randomised 2:1 to receive a 50 mg IM (anterolateral thigh) MEDI8897 dose (N = 1,000) or N-saline placebo (N = 500). Randomisation was stratified by hemisphere and subject age at randomisation (i.e. ≤3 mths, >3 to ≤6 mths, and >6 mths). Enrolment of infants > 6 mths of age was limited to ≈500. All infants followed for approximately 360 days after dosing.

Statistical methods and sample size

The sample size of 1,500 subjects was necessary based on advice from the FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size had approximately > 99% power to detect 70% RRR, assuming a placebo group medically attended RSV LRTI incidence of 8%. Power calculations were based on a Poisson regression model with robust variance[6] comparing MEDI8897 50 mg versus placebo, with 2-sided, $\alpha = 0.05$.

For further details, please refer to the CER.

Participant flow

1540 subjects were screened, of whom 1453 subjects were randomly assigned to placebo (n = 484) or MEDI8897 (n = 969). Of the 1,453 randomised subjects, 481 in the placebo group and 966 in the MEDI8897 group were dosed. The majority of subjects completed the Day 151 efficacy follow-up (472 subjects [97.5%], placebo; 945 subjects [97.5%], MEDI8897. A total of 454 subjects (93.8%) randomised to placebo and 913 subjects (94.2%) randomised to MEDI8897 completed the study. (Clinical study report)

[6] Zou G, Am J Epidemiol. 2004;159(7):702-6.

Efficacy results

Incidence of Medically Attended RSV-confirmed LRTI Through 150 Days Post Dose (ITT Population) (Table 13, Clinical study report)

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

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

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

Single dose of 50 mg IM MEDI8897 resulted in a RRR in the incidence of medically attended RSV-confirmed LRTI through 150 days post dose of 70.1% (95% CI: 52.3%, 81.2%) when compared to placebo (p <0.0001). Similar results were seen based on the same primary analysis model in the PP population and the supporting analysis models (Poisson regression with robust variance with adjustment of follow-up time and stratified CMH test) in the ITT population.

Subgroup analyses of the primary efficacy endpoint (incidence of medically attended RSV confirmed LRTI through 150 days post dose) showed consistent results for hemisphere, age at randomisation, weight at birth, weight at Day 1, GA, and siblings enrolled in the study. No statistically significant interactions were observed between each subgroup and treatment and RRRs through 150 days post dose, favouring MEDI8897 vs. placebo across all subgroups. While efficacy was demonstrated for infants >5 kg, it was less than that seen for the smaller-weight infants. Additional PK exposure-efficacy analyses showed that a dose of 100 mg would give similar exposures for infants ≥5 kg with a predicted improvement in efficacy. (CER p27)

Results for the secondary efficacy endpoints

The incidence rates of the RSV-confirmed LRTI hospitalisation were lower in the MEDI8897 group than the placebo group for all age at onset categories.

Pharmacokinetics

The serum concentrations decayed monoexponentially beyond the Day 91 sampling timepoint without any sign of PK nonlinearity. On Day 151, 97.8% (851/833) of MEDI8897 serum concentrations were above the targeted 90% effective concentrations threshold of 6.8 µg/mL. Additionally, due to the overlapping exposures, there was no difference in serum concentrations profiles of individuals who were ADA-positive or negative at any time during the entire follow-up period. (CER p27)

Immunogenicity

Of those with samples available, ADA was detected post baseline in 3.8% (18/469) of subjects (placebo group) and 5.6% (52/929) (MEDI8897 group). For further details, please refer to the CER.

Safety

In the as-treated population, AE rates for the MEDI8897 group were generally comparable or lower than placebo group across the event categories. Overall, 86.8% of subjects in the placebo group and 86.2% of subjects in the MEDI8897 group had ≥1 AE.

Five deaths (3 placebo group; 2 in MEDI8897 group) were reported during the study through Day 361. One additional subject in the placebo group died on Day 367. None of these deaths were considered related to investigational product by the investigator.

There was no notable difference between the placebo and MEDI8897 groups when adverse events were analysed by either post-baseline positive or post-baseline negative anti-drug antibody status.

Conclusions

Study 3, conducted across both hemispheres, demonstrated a RRR of the incidence in MA RSV LRTI in this preterm infant population in RSV Season 1 given a single IM dose of 50mg of 70.1% (95% CI: 52.3%, 81.2%) (p <0.0001) through 150 days post dose. However, as demonstrated in the prespecified subgroup analysis of the primary endpoint by weight at dosing there was a significantly lower efficacy in the infants weighing >5 kg, with RRR of incident MA RSV LRTI through 150 days post dose of 58.5% for infants >5 kg vs. >80% for infants ≤5 kg.

For Studies 4, 5 and 8, a 100 mg dose was proposed to achieve the target exposure in infants weighing ≥5 kg in Season 1, and a 200 mg dose proposed in Season 2, based on the expected body weight range in older infants experiencing their second RSV season.

Study D5290C00004 (MELODY)[7]

Study D5290C00004 (MELODY) was a Phase 3, 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. (Clinical study report).

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	

[7] Hammit LL et al, N Engl J Med. 2022;386(9):837-846.

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. Exploratory endpoints are described in the Clinical study report.

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

Subjects were randomised 2:1 to receive a single fixed IM dose of nirsevimab (50 mg for subjects weighing < 5 kg or 100 mg for subjects weighing ≥ 5 kg at the time of dosing) or placebo. Randomisation was stratified by hemisphere (NH and SH) and by subject age at the time of randomisation (≤ 3.0 months, > 3.0 to ≤ 6.0 months, and > 6.0 months). All subjects were followed for approximately 510 days after dosing.

Sample size

The study was originally designed to analyse the primary endpoint on the full enrolment of approximately 3000 infants. However, the impact of the COVID-19 pandemic on RSV circulation led to a protocol amendment, in consultation with regulatory authorities (Type B meeting, Dec 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. As a result, the study comprises two cohorts: a Primary Cohort (1490 randomised subjects) and a complementary Safety Cohort (1522 randomised subjects). (CER p33)

Statistical methods

Please refer to the CER and published paper for a complete description of the statistical methods.

Participant flow

Primary cohort

1626 subjects were screened, with 1490 subjects 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.

All subjects

3319 subjects were screened and 3012 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.

In the Final Clinical study report, D5290C00004, it is reported that 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.

Efficacy results

Primary efficacy

Incidence of Medically attended RSV LRTI through 150 Days Post Dose in MELODY

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

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

For the primary efficacy endpoint for the Primary Cohort based on the Primary Analysis in Intention-to-treat Population 1 (ITT1), a single IM dose of nirsevimab demonstrated clinical and statistically significant efficacy with a RRR in the incidence of MA RSV LRTI through 150 days post dose of 74.53% (95% CI: 49.63%, 87.12%) versus placebo (p<0.0001). 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.

Secondary efficacy

Incidence of Medically attended RSV LRTI with Hospitalisation through 150 Days Post Dose in MELODY

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 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study as covariate for pooled studies) obtained after missing data imputation.

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

Pooled analysis (Study D5290C00003 and Study D5290C00004 (MELODY))

In the final study report, the Sponsor stated that a pre-specified pooled analysis, including Intention-to-treat Population 1(ITT1) from MELODY (Primary Cohort) and the ITT population from Study 3 (MELODY [Primary Cohort]/Study 3 Pool), was conducted to assess overall efficacy on RSV hospitalisations in both preterm and term infants. The pooled analysis was pre-specified to mitigate the risk that ITT1 from MELODY (Primary Cohort) alone would be underpowered to show a statistically significant treatment difference for this secondary efficacy endpoint, due to a shift in the management of more serious RSV disease to the outpatient setting. (Final Clinical Study report, page 238)

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 versus 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; CER, Table 13).

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; CER, Table 13). 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.

Delegate comment:

The ACM may wish to refer to the published paper for the pooled analysis of these studies.[8] The published paper also includes a description of the population pharmacokinetic analysis of the pooled data.

Pharmacokinetics (MELODY study)

Mean serum concentrations of nirsevimab, administered as a single fixed IM dose (50 mg for <5 kg weight on Day 1, 100 mg for ≥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 two weight groups.

Immunogenicity (MELODY study)

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 to 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. (Final clinical study report, page 240)

Safety (MELODY study)

Nirsevimab was well tolerated. Similar types and frequencies of treatment emergent adverse events were reported in both the nirsevimab and placebo groups. Overall, 83.7% of nirsevimab group subjects and 81.8% of placebo group subjects had at least one AE. The most common AEs (>10% of subjects in any treatment group) reported with nirsevimab (vs. placebo) were URTI (29.4% vs. 28.5%), nasopharyngitis (20.4% vs. 21.5%), pyrexia (12.4% vs. 10.3%), and dermatitis diaper (nappy rash) (10.5% vs. 9.2%). The majority of AEs were Grade 1 or Grade 2 in severity. The most common Grade 3 AEs reported with nirsevimab vs. placebo were bronchiolitis (0.5% vs. 0.8%), RSV bronchiolitis (0.2% vs. 0.5%), bronchitis (0.1% vs. 0.3%), pneumonia (0.3% vs. 0.1%), and gastroenteritis (0.2% vs. 0.0%). Grade 4 or 5 events occurred in ≤1% of subjects in either group. (CER p38)

In their Milestone 5 response, the Sponsor stated that in MELODY (All Subjects, AT population), safety data from both the Primary and Safety Cohorts combined included all available safety data through 360 days post dose for all subjects at the time of database lock. The incidences of AEs, AEs of ≥ Grade 3 severity, SAEs, SAEs of ≥ Grade 3 severity, treatment-related skin reactions, and NOCDs were similar in the nirsevimab and placebo groups. There were four AESIs in the nirsevimab group (all treatment related skin hypersensitivity events and none were SAEs) and none in the placebo group. Four treatment-emergent deaths due to medical conditions occurred in the nirsevimab group (none in the placebo group); one additional death occurred in a subject prior to randomisation/dosing and one further death occurred due to a road traffic accident after Day 360 in a subject who received nirsevimab. Treatment-emergent SAEs occurred in 7.5% of subjects in the nirsevimab group and 8.3% in the placebo group. No deaths or SAEs were considered by the investigator to be related to nirsevimab.

Season 2

Monitoring of disease incidence from the second RSV season (Day 362 to Day 511) in MELODY did not show any increase in cases of MA RSV LRTI and no increased severity of disease for subjects administered nirsevimab compared to subjects administered placebo. The Sponsor highlighted that there was no evidence to support the theoretical risk of antibody dependent enhancement of disease with nirsevimab. (Final clinical study report page 242)

[8] Simões E et al, Lancet Child Adolesc Health 2023; 7: 180–89

Summary of Incidence of Medically attended (MA) RSV LRTI (Protocol Defined), RSV LRTI Hospitalisation (Protocol Defined), MA RSV LRTI (Very Severe), All MA RSV LRTI, All MA RSV (Any Test) LRTI, All MA RSV Respiratory Illness with Hospitalisation, All MA RSV (Any Test) Respiratory Illness with Hospitalisation, All MA LRTI (Any Cause), All MA Respiratory Illness with Hospitalisation (Any Cause) from 361 through 510 Days Post Dose (All Subjects), Table 77, Final Clinical study report

Subjects with	Number (%) of subjects	
	Placebo (N = 1003)	Nirsevimab (N = 2009)
MA RSV LRTI (protocol defined)	10/967 (1.0)	19/1944 (1.0)
MA RSV LRTI hospitalisation (protocol defined)	3/967 (0.3)	3/1944 (0.2)
MA RSV LRTI (very severe)	3/967 (0.3)	3/1944 (0.2)
All MA RSV LRTI	18/967 (1.9)	30/1944 (1.5)
All MA RSV (any test) LRTI	20/967 (2.1)	35/1944 (1.8)
All MA RSV respiratory illness with hospitalisation	4/967 (0.4)	6/1944 (0.3)
All MA RSV (any test) respiratory illness with hospitalisation	6/967 (0.6)	10/1944 (0.5)
All MA LRTI (any cause)	71/967 (7.3)	134/1944 (6.9)
All MA respiratory illness with hospitalisation (any cause)	11/967 (1.1)	21/1944 (1.1)

The incidence rate was calculated using the number of ITT subjects who were followed up for at least 361 days post dose as the denominator.

ITT = intent-to-treat; LRTI = lower respiratory tract infection; MA = medically attended; N = number of subjects in treatment group; RSV = respiratory syncytial virus.

Delegate comment

The final study report was provided with the response to Milestone 5 (13th July 2023), therefore additional data have been made available since the completion of the Round 2 clinical evaluation report.

The Delegate concurs with the Clinical evaluator that despite the challenges posed by the COVID-19 pandemic, and the amended sample size, the primary objective based on the Primary Cohort was met. In term and late preterm infants ≥35 weeks gestational age (MELODY [Primary Cohort]), nirsevimab demonstrated statistically significant clinical efficacy (RRR 74.5%; 95% CI 49.6%, 87.1%; p<0.0001) against the primary endpoint Medically attended RSV LRTI. Results were consistent in the exploratory analysis in MELODY (All Subjects).

Serum concentrations declined in a linear fashion after 31 days post dose in all subjects, with a substantial overlap in concentrations between weight groups. Safety analyses showed that nirsevimab was safe and well tolerated.

Study D5290C00005 (MEDLEY)[9]

Study D5290C00005 (MEDLEY) was a pivotal Phase 2/3 randomised, double-blind, palivizumab-controlled study to evaluate the safety, pharmacokinetics (PK), anti-drug antibody (ADA) response, and descriptive efficacy of nirsevimab in high-risk infants eligible to receive palivizumab when entering their first or second respiratory syncytial virus (RSV) season (Season 1 or Season 2, respectively).

[9] Domachowske J et al, N Engl J Med 2022;386(9):892-4.

Objectives and Endpoints

Objectives	*Endpoints*
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
Secondary	
PK To evaluate serum concentrations of nirsevimab and palivizumab	• Nirsevimab and palivizumab serum concentrations • Summary of nirsevimab serum concentrations
ADA To evaluate ADA responses to nirsevimab and to palivizumab in serum	Incidence of ADA to nirsevimab and palivizumab in serum
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

ADA = anti-drug antibody; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; 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; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Exploratory objectives and associated endpoints are described in the CER and Clinical study report.

Study design

Approximately 900 palivizumab-eligible infants entering their first RSV season were planned to be enrolled into 1 of 2 cohorts: (1) preterm cohort, including approximately 600 preterm infants (≤ 35 weeks gestational age) without chronic lung disease (CLD)/congenital heart disease (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. Within each cohort, randomisation was stratified by hemisphere (northern, southern) and subject age at the time of Season 1 randomisation (≤ 3 months, > 3 to ≤ 6 months, > 6 months). In Japan, the CLD/CHD cohort included subjects with Down syndrome alone who are palivizumab-eligible in this country.

Statistical methods and sample size

There were three planned analyses for this study: primary analysis, Season 2, and the final analysis:

The primary analysis was conducted after all randomised subjects had completed follow-up through the first 5 month RSV season (i.e. Season 1 Day 151 visit) and included all available Season 1 safety, efficacy, PK, and ADA data at the time of data cut-off.

The Season 2 analysis was conducted after all CLD/CHD subjects had completed follow-up through the second 5 month RSV season (i.e. Season 2 Day 151 visit) and included all available Season 1 data and Season 2 safety, efficacy, PK, and ADA data at the time of data cut-off.

The final analysis presented safety, efficacy, PK, and ADA data at the time of the database lock (22 February 2023) and was triggered after all subjects from the CLD/CHD cohort completed follow-up through 360 days post first dose in Season 2 and also included all available Season 1 data (through 360 days post first dose in Season 1). (Final CSR p4)

Delegate comment:

The global clinical study protocol was amended to update the sample size for target enrolment from that originally planned, due to the challenges of enrolment during the COVID-19 pandemic. The study was paused in the Southern Hemisphere in March 2020 and the clinical study protocol was amended in consultation with Health Authorities to reduce the sample size from the originally planned target of 1500 to 900. The study resumed in the Northern Hemisphere in October 2020 and enrolment subsequently concluded. (Final CSR p274)

Season 1

In Season 1, all subjects were randomised 2:1 to either nirsevimab (approximately 600 subjects, including approximately 400 subjects in the preterm cohort and approximately 200 subjects in the CLD/CHD cohort) or palivizumab (approximately 300 subjects, including approximately 200 subjects in the preterm cohort and approximately 100 subjects in the CLD/CHD cohort). Subjects in the nirsevimab group received a single fixed intramuscular (IM) dose of nirsevimab followed by 4 once-monthly IM doses of placebo. The nirsevimab dose level was stratified by weight band, ie, 50 mg for infants weighing < 5 kg or 100 mg for infants weighing ≥ 5 kg. Subjects in the palivizumab group received 5 once-monthly IM doses of 15 mg/kg palivizumab. (Final clinical study report)

Season 2

The Season 2 study population comprised approximately 300 subjects from the CLD/CHD cohort who had already participated in Season 1. Subjects from the CLD/CHD cohort who were randomised to nirsevimab in Season 1 received a second dose of nirsevimab in Season 2 (approximately 200 subjects) (referred to as the NIRS/NIRS group). Subjects from the CLD/CHD cohort who were randomised to palivizumab in Season 1 were re-randomised 1:1 to nirsevimab or palivizumab (approximately 50 subjects in each group) (referred to as the PALI/NIRS and PALI/PALI groups, respectively). Subjects in the Season 2 nirsevimab groups received a single fixed IM dose of 200 mg nirsevimab (as 2 injections of 1 ml at separate sites) followed by 4 once-monthly IM doses of placebo. Subjects in the palivizumab group received 5 once-monthly IM doses of 15 mg/kg palivizumab. (Final clinical study report)

Delegate comment: please refer to the CER Figure 3 and 4 for a flowchart of the study design and dosing schedule. Season 2 included the chronic lung disease (CLD)/congenital heart disease (CHD) cohort only.

Participant flow

Season 1

A total of 925 high-risk subjects were randomised overall (616 to nirsevimab, 309 to palivizumab), including 615 subjects in the preterm cohort (612/615 were dosed) and 310 subjects in the CLD/CHD cohort (306/310 dosed). (Final CSR)

Season 2

In Season 2, a total of 262 subjects from the Season 1 CLD/CHD cohort proceeded into the Season 2 phase of the study. Those subjects from the CLD/CHD cohort who had received nirsevimab in Season 1 received a second dose of nirsevimab in Season 2 (n = 180; the NIRS/NIRS group). Those subjects from the CLD/CHD cohort who received palivizumab in Season 1 were randomised 1:1 to a second course of palivizumab (n = 42; the PALI/PALI group) or to nirsevimab (n = 40; the PALI/NIRS group) in Season 2. (Final CSR)

Safety

Primary analysis

Through to 360 days post first dose in Season 1, nirsevimab had a similar AE profile compared palivizumab, in the overall population and preterm and CLD/CHD cohorts, including infants with CLD, CHD, and those born <29 weeks GA. Types and frequencies of AEs were generally balanced between the nirsevimab and palivizumab groups, with a low incidence of IP-related events (including IP-related skin reactions), investigator assessed AESIs, and NOCDs.

Overall Summary of treatment emergent adverse events for Overall Population, Preterm and CLD/CHD Cohorts through 360 Days Post in MEDLEY First Dose in Season 1 – As-treated Population (Season 1) (CER Table 18)

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivizumab (N = 304)	Nirsevimab (N = 614)	Palivizumab (N = 206)	Nirsevimab (N = 406)	Palivizumab (N = 98)	Nirsevimab (N = 208)
≥1 IP-related event of ≥Grade 3 [b]	0	0	0	0	0	0
Any AE with outcome death	1 (0.3)	5 (0.8)	0	2 (0.5)	1 (1.0)	3 (1.4)
≥1 serious [c] event	38 (12.5)	80 (13.0)	13 (6.3)	35 (8.6)	25 (25.5)	45 (21.6)
≥1 serious [c] and/or ≥Grade 3 [b] event	39 (12.8)	84 (13.7)	13 (6.3)	35 (8.6)	26 (26.5)	49 (23.6)
≥1 IP-related serious [c] event	0	0	0	0	0	0
≥1 AESI based on investigator assessments	0	3 (0.5)	0	1 (0.2)	0	2 (1.0)
≥1 AESI based on selected MedDRA PT codes	47 (15.5)	117 (19.1)	32 (15.5)	68 (16.7)	15 (15.3)	49 (23.6)
≥1 IP-related AESI based on selected MedDRA PT codes	1 (0.3)	2 (0.3)	1 (0.5)	1 (0.2)	0	1 (0.5)
≥1 IP-related skin reaction	2 (0.7)	2 (0.3)	1 (0.5)	1 (0.2)	1 (1.0)	1 (0.5)
≥1 NOCD	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)
≥1 IP-related NOCD	0	0	0	0	0	0
≥1 event related to COVID-19	6 (2.0)	17 (2.8)	2 (1.0)	11 (2.7)	4 (4.1)	6 (2.9)
≥1 confirmed COVID-19 [d]	6 (2.0)	15 (2.4)	2 (1.0)	10 (2.5)	4 (4.1)	5 (2.4)
≥1 suspected COVID-19	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)

[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).

Season 2

The adverse event profile was similar across the treatment groups (NIRS/NIRS, PALI/NIRS, and PALI/PALI), with the types and frequencies of AEs being generally balanced (CER, Table 19).

The numbers of subjects in the as-treated population in the PALI/NIRS (n=40) and PALI/PALI (n=42) groups was lower than in the NIRS/NIRS group (n=180). The incidence of AESIs was low and balanced between treatment groups in the CLD/CHD Cohort in Season 2. The incidence of ≥Grade 3 events and SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than the PALI/PALI group; however, this was not observed within all analysed time points through 30 days post first dose. (CER p48)

In the final study report, it is stated that 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 IP-related AEs, IP-related NOCDs, or investigator-assessed skin hypersensitivity in any treatment group. No deaths occurred in Season 2. (Synopsis, final CSR)

Summary of Season 2 Safety Results (Through 360 Days Post First Dose in Season 2),

Through 360 days post first dose in Season 2, the AE profile was similar across the treatment groups (NIRS/NIRS, PALI/NIRS, and PALI/PALI), with the types and frequencies of AEs being generally balanced. The number of subjects in the As-treated Population in the PALI/NIRS (n = 40) and PALI/PALI (n = 42) groups was lower than in the NIRS/NIRS group (n =180).

In the final Clinical Study Report, it was noted that 'in the CLD and CHD subpopulations, the only notable difference between the treatment groups was that in the CHD subpopulation, AESIs based on selected MedDRA PTs occurred at a numerically higher rate in the NIRS/NIRS (26.8% [15/56 subjects]) and PALI/NIRS (21.4% [3/14 subjects]) treatment groups compared with PALI/PALI (9.1% [1/11 subjects]). However, this imbalance was not observed within all analysed time points through 30 days post first dose in Season 2.'

(Final clinical study report, Synopsis)

Efficacy results

Primary analysis

Incidence of MA RSV LRTI through 150 days post first dose in Season 1 was low and balanced: 0.6% (4/616 subjects) nirsevimab group vs. 1.0% (3/309 subjects) palivizumab group. Overall disease incidence in each of the nirsevimab and palivizumab groups was distributed between the preterm cohort (0.5% [2/407 subjects] vs. 0.5% [1/208 subjects]) and CLD/CHD cohort (1.0% [2/209 subjects] vs 2.0% [2/101 subjects]). The incidence of MA RSV LRTI with hospitalisation through 150 days post first dose in Season 1 was 0.3% (2/616) nirsevimab group vs. 0.6% (2/309) palivizumab group. All of these events occurred in the CLD/CHD cohort (1.0% nirsevimab [2/209], 2.0% palivizumab [2/101]).

Season 2 analysis

In the overall population, there was no MA RSV LRTI or MA RSV LRTI with hospitalisation through 150 days post first dose in Season 2 in any treatment group. Season 2 MA LRTI (any cause) was low in all three treatment groups.

Final analysis

There were no instances of MA RSV LRTI through 150 days post first dose in Season 2 in any treatment group.

There were no instances of MA RSV LRTI with hospitalisation through 150 days post first dose in Season 2 in any treatment group. There was one subject with MA RSV LRTI with hospitalisation (subtype RSV B; 1/ 40 [2.5%] in the PALI/PALI group occurring from 151 through 361 days post first dose in Season 2.

Incidence of Medically attended RSV LRTI by RSV Subtype and Reporting Period in Season 2 – ITT Population (Table 30, Final CSR)

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]	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)
Through 360 days post first dose	1 (2.4)	1 (2.5)	0
RSV A	0	1 (2.5)	0
RSV B	1 (2.4)	0	0

Pharmacokinetics

In both Season 1 and 2, nirsevimab 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 the weight-band dose in Season 1 and the fixed dose in Season 2.

Immunogenicity

'Safety was assessed in Season 2 and Season 1 + Season 2 combined in the NIRS/NIRS group by post-baseline ADA status. Anti-drug antibodies in either Season 1 or Season 2 in this group did not appear to impact safety through 360 days post first dose in Season 2. Additionally, no hypersensitivity or other AESI was reported in Season 2 for this group or any treatment group.

Amongst the 40 subjects who received palivizumab in their first RSV season followed by nirsevimab in their second RSV season and had samples available for analysis, post-baseline ADA against nirsevimab was observed in a single subject (2.5%); this subject completed the study and had no IP-related AEs, AESIs, or skin hypersensitivity reactions through 360 days post nirsevimab dose.

There was no apparent impact of ADA on PK through 150 days post dose. Due to a limited number of ADA-positive subjects with MA RSV LRTI in both seasons, the impact of ADA efficacy could not be evaluated.' (Final CSR, synopsis)

Evaluator conclusions

The MEDLEY study using weight-based dosing of single dose 50mg or 100mg demonstrated that nirsevimab had comparable safety and tolerability profile to palivizumab, in the overall population of preterm infants, and those with CLD and/or CHD in Season 1, and with comparable safety findings for subjects with CLD/CHD who received nirsevimab (single IM dose of 200mg) in Season 2.

The evaluator highlighted that there was no evidence of immune priming in subjects who had received prior nirsevimab, and no evidence that the second dose of nirsevimab boosted ADA responses in those few subjects who were ADA positive to nirsevimab in Season 1. In both seasons, based on limited data, there was no apparent impact of ADA against nirsevimab on PK and efficacy.

The Delegate concurs with the evaluator that the lack of either MA RSV LRTI or MA RSV LRTI with hospitalisation through 150 days post the Season 2 Day 1 dose may reflect the impact of

public health measures against COVID-19 impacting on lower rates of circulating RSV. (see questions for ACM)

Study D5290C00008 (MUSIC)

Study D5290C00008 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.

Objectives and Endpoints

Objectives	***Endpoints***
Primary	
To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age.	All TEAEs, TESAEs, AESIs, and NOCDs.
Secondary	
To evaluate the PK of nirsevimab.	Summary of nirsevimab serum concentrations.
To evaluate ADA responses to nirsevimab in serum.	Incidence of ADA to nirsevimab in serum.
To assess the efficacy of nirsevimab when administered as a single IM dose to infants ≤ 24 months of age.	Incidence of MA LRTI (inpatient and outpatient) and hospitalisations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab

Exploratory outcomes are described in the CER and Clinical study report.

Study design

Inclusion criteria

1. Neonate, infant, or young child ≤24 months of age who, per Investigator judgment, are: (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

2. The subject must meet at least 1 of the following conditions at the time of informed consent:

(a) Diagnosed with combined immunodeficiency (severe combined immunodeficiency, cross-linked hyper IgM syndrome, etc.); antibody deficiency (crosslinked agammaglobulinemia, common variable immunodeficiency, non-crosslinked hyper IgM syndromes, etc.); or other immunodeficiency (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc.).

(b) Diagnosed with HIV infection.

(c) History of organ or bone marrow transplantation.

(d) Subject was receiving immunosuppressive chemotherapy.

(e) Subject was receiving systemic high-dose corticosteroid therapy (prednisolone equivalents ≥ 0.5 mg/kg every other day, other than inhaler or topical use).

(f) Subject was receiving other immunosuppressive therapy (eg, azathioprine, methotrexate, mizoribine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus, cytokine inhibitors, etc.).

Statistical methods and sample size

Sample size was expanded to 100 planned to receive a single IM dose of nirsevimab to evaluate the safety, PK, ADA, and efficacy, and assessed descriptively. To evaluate risk, a sample size of 100 subjects exposed to nirsevimab in this Phase II study would provide a 95% probability of observing at least 1 AE if the true event rate is 3%; if no AEs were observed, this study provides 95% confidence that the true event rate is ≤3%. (CER p51)

There were three planned analyses for this study: two interim analyses and a final analysis.

Participant flow

100 subjects were 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. (Final CSR)

'Subjects could have had more than one immunocompromising condition. Approximately one third of the subjects (33 [33.0%] subjects) met inclusion criterion 2a (diagnosed with primary immunodeficiency); 29 (29%) subjects met inclusion criterion 2e (receiving systemic high-dose corticosteroid therapy), 20 (20.0%) subjects met inclusion criterion 2d (receiving immunosuppressive chemotherapy), 16 (16.0%) subjects met inclusion criterion 2c (history of organ or bone marrow transplantation), 15 (15.0%) subjects met inclusion criterion 2f (receiving other immunosuppressive therapy), and 8 (8.0%) subjects met inclusion criterion 2b (diagnosed with HIV).'

(Final CSR, Synopsis)

Safety

In total, 81 (81.0%) subjects experienced at least 1 TEAE; the most commonly reported TEAEs were in the SOCs of Infections and infestations (73 [73.0%] subjects), Skin and subcutaneous tissue disorders (42 [42.0%] subjects), and Gastrointestinal disorders (33 [33.0%] subjects).

Overall, the incidence of Grade 1 (22 [22.0%] subjects), Grade 2 (24 [24.0%] subjects), and Grade 3 (28 [28.0%] subjects) TEAEs was similar among the subjects. The incidence of Grade 4 and Grade 5 TEAEs was low (4 [4.0%] subjects and 3 [3.0%] subjects, respectively). Three (3.0%) subjects experienced a TEAE with the outcome of death (LRTI, septic shock, and tumour haemorrhage); these events were not considered related to the IP. No subjects experienced a NOCD.

Five (5.0%) subjects experienced AESIs based on Investigator assessment; all of which were assessed as skin hypersensitivity reactions. None of the AESIs based on Investigator assessment occurred within 1 day of IP administration.

(Final CSR, Synopsis)

Efficacy results

In the final CSR, it is reported that none of the MA RSV LRTI met the criteria of a protocol-defined MA RSV LRTI during the study; there were no RSV positive events by either local or central testing reported through 150 days post dose.

Through 150 to 361 days post dose, there was a low incidence of other (non-protocol-defined) MA RSV LRTI.

Pharmacokinetics

Mean nirsevimab serum concentrations were higher in those subjects who received 200 mg nirsevimab than in those who received 50 mg or 100 mg nirsevimab, but with substantial overlap between the two groups. Fourteen (14.0%) subjects experienced a more rapid decline in serum nirsevimab concentration over time. The majority of these subjects had evidence of protein-losing conditions.

Immunogenicity

Of the 97 subjects with available samples for ADA assessment through to Day 361 post dose, 11/97 (11.3%) subjects developed treatment-emergent ADAs during the study. All 11 (11.3%) subjects were positive for ADA against the YTE substitution, and 1 (1.0%) subject was positive for neutralising ADAs. (Synopsis, Final CSR)

Delegate comments

Results from this study have been updated with the availability of the final Clinical Study report. Although numbers were small, the Delegate concurs with the evaluator that nirsevimab was well tolerated in this population.

The evaluator noted that there were no protocol-defined MA RSV LRTIs reported, which may be a reflection of the impact on public measures to curtail COVID-19 reducing RSV transmission. Efficacy results were descriptive only and it is noted that the Sponsor is seeking approval in children with certain conditions eg neuromuscular disease and congenital airway anomalies which were not included in this study.

Safety

The safety analyses for this application are discussed in detail in the CER and included in the above summaries for each of the phase 2 and 3 studies. The safety discussion in the Overview will highlight results from the pooled analysis of the Melody and Study 3, adverse events of special interest and some additional comments from the FDA Integrated review.

The nirsevimab clinical development programme included a Phase I study in adults and a Phase Ib/IIa study in preterm infants, 3 pivotal studies in infants and children, and an open-label study in immunocompromised infants and children.

Safety data were available from 3680 subjects dosed with nirsevimab (3284 subjects receiving the proposed dose).

Integrated safety analyses (MELODY) (All Subjects)/Study 3 (Proposed Dose) Safety Pool

Safety data from MELODY and Study 3 were pooled, as these studies were placebo-controlled, randomised, double-blind, studies that used the same safety endpoints and included healthy infant populations. The inclusion/exclusion criteria of these two studies are also similar, except for gestational age. Subjects randomised to nirsevimab received a dose of 50 mg IM for subjects with weight <5 kg at dosing or 100 mg for subjects with weight ≥5 kg at time of dosing in MELODY. In Study 3, all subjects randomised to nirsevimab received a dose of 50 mg IM.

MELODY (All subjects)/Study 3 (Proposed Dose) Safety Pool (3854 subjects dosed with nirsevimab [N=2570] or placebo [N=1284])

A subpopulation of the pooled analysis included pooled data of all dosed subjects from MELODY Primary and Safety Cohorts and dosed subjects weighing <5 kg at the time of dosing from Study 3. This was considered the most relevant summaries of safety data to evaluate the adverse event profile. (CER p58)

In the safety pool of infants born at term and preterm (≥29 weeks GA), the percentage of subjects with AEs in the nirsevimab group was generally comparable to those in the placebo group across the event categories (CER table 22). Overall, 84.0% of nirsevimab group and 82.6% of placebo group had at least one AE.

The evaluator concluded that across the five studies (Studies 2 and 3, MELODY, MEDLEY and MUSIC) conducted in the target population, nirsevimab at the single doses administered (50mg or 100mg) IM appeared to be safe.

In the few infants entering their second RSV season in MEDLEY and MUSIC, the 200mg IM dose appeared safe. There were no safety concerns in the very and moderately pre-term infants (Study 2), preterm infants (<35wGA), infants with chronic heart or lung problems (MEDLEY) and immunocompromised infants (MUSIC).

ADA positivity to nirsevimab was generally low, and when it did occur was not associated with altered nirsevimab PK, or any safety signal.

In the small number of subjects who received a second dose on 200mg IM in Season 2, there was no evidence of priming if they had received nirsevimab in RSV Season 1 or boosting of an anamnestic response based on their Season 1 and Season 2 immunogenicity data.

The recently published FDA Integrated review[10] (page 5) also highlighted that the available safety data from the clinical trials demonstrate that nirsevimab is safe for its intended use. 'Severe or serious hypersensitivity reactions, such as anaphylaxis, and serious skin reactions were not reported in the nirsevimab clinical trials. Although a numerical imbalance in the incidence of death is noted in the nirsevimab clinical trials (12 deaths among subjects who received nirsevimab vs. 4 deaths in subjects who received the control), the overall incidence of deaths was similar between the two arms. No organ-specific toxicity was identified that could have contributed to or resulted in deaths.'

Risk Management Plan (RMP) evaluation

Sanofi-Aventis Australia Pty Ltd submitted EU-RMP version 1 succession 4 (dated 7 September 2022; DLP 3 May 2021) and ASA version 1 succession 1 (dated 28 September 2022) in support of this application. In the Section 31 response, the sponsor submitted EU-RMP version 2 succession 1 (dated 23 March 2023; DLP 9 November 2022). There was no change to the ASA version.

The summary of safety concerns are outlined in the following table.

Summary of safety concerns		**Pharmacovigilance**		**Risk Minimisation**	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	None	–	–	–	–
Missing information	Long term safety	✓	✓*	–	–

*Studies D5290C00004 (MELODY) and D5290C00005 (MEDLEY)

Following the Round 2 evaluation, there were no new or outstanding recommendations.

The sponsor will provide a revised ASA once the final CSRs have been submitted to TGA. This is acceptable.

The Delegate notes that the final reports for studies D5290C00004 (MELODY) and D5290C00005 (MEDLEY) have been provided with the response to Milestone 5.

[10] FDA Integrated review 761328Orig1s000
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761328Orig1s000IntegratedR.pdf

RMP evaluator recommendations regarding conditions of registration:

The suggested wording for conditions of registration is:

The BEYFORTUS EU-Risk Management Plan (RMP) (version 2 succession 1, dated 23 March 2023, data lock point 9 November 2022), with Australian Specific Annex (version 1 succession 1, dated 28 September 2022), included with submission PM-2022-04428-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The wording for the PSUR requirement is included in the RMP Round 2 report.

As BEYFORTUS is a new biological entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

BEYFORTUS (nirsevimab) is to be included in the Black Triangle Scheme. The PI and CMI for BEYFORTUS must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Discussion

The Sponsor has submitted a comprehensive dossier to support registration of nirsevimab in Australia. Discussion of the wording of the indication is warranted, specifically the high-risk groups to be included, acknowledging the small number of infants in the MEDLEY and MUSIC studies and the extrapolation of efficacy to high-risk subgroups.

The impact of public measures to curtail COVID-19 reducing RSV transmission has been raised by the Clinical evaluator as potentially impacting the low rates of medically attended RSV in several of the clinical studies, with the COVID-19 pandemic significantly altering the epidemiology of RSV. Atypical RSV seasons have occurred in Australia with the COVID-19 pandemic and related lockdowns[11] and highlighted by the clinical evaluator as a potential concern for efficacy of a single dose of nirsevimab in the event of a prolonged RSV season. This has been addressed satisfactorily by the Sponsor in their Section 31 Response but remains a concern for which ongoing epidemiological surveillance is needed.

The potential for resistance to nirsevimab and that variants with reduced susceptibility to nirsevimab will emerge and become prevalent in the future is an area of uncertainty. The Sponsor has outlined sponsored RSV Molecular Surveillance Studies they are undertaking, including OUTSMART-RSV, INFORM-RSV (with one site in Australia), and SEARCH-RSV surveillance programs in their Section 31 Response.

The FDA Integrated review[10] has highlighted that with the development of maternal RSV vaccines for passive immunisation of infants, it is not known whether use of nirsevimab in such infants who have received passive immunisation by maternal RSV vaccination will provide added benefit. The FDA also noted that shifting of severe RSV disease to children's second RSV season is a potential risk, with long term data needed to fully assess this.

It is not yet known which groups will meet eligibility criteria for funding for nirsevimab, which will ultimately guide implementation of a program for prevention of RSV in neonates, infants and children in Australia.

Conclusions

The submitted data are sufficient to recommend approval of this application. The final wording of the indication will be determined following ACM. Approval of this application is subject to

[11] Eden at al 2022, Nature Communications. 2022;13(1):2884.

implementation of the quality and risk management plan conditions of registration and satisfactory resolution of the product information.

References/attachments for ACM

Number	Document name	Location/ID	ACM attachment
1	Round 2 Clinical evaluation report (TGA copy)	D23-5482073	☒
2	Module 3 Quality Product Summary	D23-2382519	☒
3	Non-clinical evaluation report (TGA copy)	D23-5259876	☒
4	Round 2 RMP evaluation (Sponsor copy)	D23-2100751	☒
5	Population pharmacokinetics Review (TGA copy)	D23-5440411	☒
6	Published paper for Study 3	D23-3242741	☒
7	Published paper for MELODY study (NEJM 2022)	D23-3242824	☒
8	Published paper for MELODY study (NEJM 2023)	D23-3242858	☒
9	Published paper for pooled analysis of Study 3 and MELODY	D23-3242773	☒
10	Published paper for MEDLEY	D23-3242801	☒
11	FDA Integrated Review 761328Orig1s000	D23-3242922	☒

Appendix 1: Review of the Product Information

The following recommendations refer to the PI, version beyfo-ccdsv4-piv1-d5-ann-12jul23, submitted with the Milestone 5 response. The proposed PI has been compared to the approved PI for the FDA, Health Canada and the EMA.

The Delegate acknowledges that the proposed PI for Australia has been updated with relevant results from the completed clinical study reports for the MEDLEY, MUSIC and MELODY trials. (Milestone 5 response, 13 July 2023)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The wording of the indication will be finalised following ACM.

The Delegate proposes an alternative wording for Australia, consistent with the FDA indication and acknowledging use according to 'official recommendations.'

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

-Neonates and infants born during or entering their first RSV season.

-Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.

Beyfortus should be used in accordance with official recommendations.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosing recommendations

Please adopt the format and headings of the FDA PI for this section, as the distinct recommendations for children undergoing cardiac surgery with cardiopulmonary bypass are clearer to the prescriber.

Please include the paragraphs in the Eu SmPC (Section 4.2) and the Health Canada Product monograph (section 1.1) relating to the limitations of the data:

Dosing in infants with a body weight from 1.0 kg to <1.6 kg is based on extrapolation, no clinical data are available. Exposure in infants <1 kg is anticipated to yield higher exposures than in those weighing more. The benefits and risks of nirsevimab use in infants <1 kg should be carefully considered.

There are limited data available in extremely preterm infants (Gestational Age [GA] <29 weeks) less than 8 weeks of age. No clinical data are available in infants with a postmenstrual age (gestational age at birth plus chronological age) of less than 32 weeks (see section 5.1).

There are no safety and efficacy data available on repeat dosing.

The safety and efficacy of nirsevimab in children aged 2 to 18 years have not been established. No data are available.

Limited data are available in infants with Down syndrome (n=13), Cystic fibrosis (n=5), Congenital airway anomalies (n=9), and Neuromuscular disease (n=0; not evaluated in clinical trials).

Please see the Questions for the Sponsor regarding a minimum time frame between receiving the first and second dose of BEYFORTUS for vulnerable children up to 24 months of age.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Please include the paragraph from the FDA PI in relation to palivizumab. This could be included under an additional subheading, 'Co-administration with immunoglobulin products.'

4.6 FERTILITY, PREGNANCY AND LACTATION

Please include the Pregnancy category B2, recommended by the TGA non-clinical evaluator.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

In clinical trials

Please correct the error in the first paragraph of this section:

'…consensus nirsevimab resistance-associated substitution..'

Immunogenicity

Please correct the error in the second paragraph:

'Of 180 subjects who received nirsevimab in two consecutive RSV season's'

Clinical trials

Please include table 3 from the FDA PI, as it provides an overview of the included pivotal studies. The tables should include the final participant numbers from the MELODY and MEDLEY studies

Please include tables 5 and 6 from the Health Canada Product monograph, as they provide the stratification by subgroup for the pivotal studies. Please also ensure that these tables have been updated with final participant numbers from the MELODY and MEDLEY studies.

CMI

Please ensure that the CMI, doc ID-004869203 v2, submitted with the Section 31 Response is updated to be consistent with the PI.

Therapeutic Goods Administration

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https://www.tga.gov.au

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Nonclinical Evaluation Report

Nirsevimab [BEYFORTUS]

Submission No: PM-2022-04428-1-2
Sponsor: AstraZeneca Pty Ltd

August 2023

TGA Health Safety Regulation

NONCLINICAL EVALUATION REPORT

Submission type: New biological entity
Sponsor: AstraZeneca Pty Ltd
Generic name: **Nirsevimab**
Trade name: **BEYFORTUS**
Dose form and strength: Solution For Injection; 50 mg in 0.5 mL100 mg in 1 mL
Drug class: Recombinant human mAb against RSV A/B

Submission No: PM-2022-04428-1-2
Tox file No: E22-620584
TRIM reference: D23-5259876

Evaluator: s22 [redacted]
Date authorised: 31 August 2023

Note: This evaluation report has been peer-reviewed. This version of the document contains confidential information (this page) and is not authorised for release to the sponsor. A redacted version for external release is provided separately.

TABLE OF CONTENTS

SUMMARY, CONCLUSIONS AND RECOMMENDATION

- AstraZeneca Pty Ltd has applied to register a new biological entity, nirsevimab (BEYFORTUS), a monoclonal antibody against respiratory syncytial virus (RSV) subtype A and B, for the treatment of lower respiratory tract disease in infants and children. For infants in their first RSV season the recommended dose is 50 mg for < 5 kg b.w., 100 mg for > 5 kg b.w., and 200 mg for children who remain vulnerable to severe RSV disease entering their second RSV season (administered as 2 x intramuscular injections of 100 mg).

- The submitted Module 4 dossier was in accordance with relevant ICH guideline for nonclinical assessment of biological medicines (ICH S6[R1]). The overall quality of the nonclinical dossier was good. The pivotal safety-related studies were GLP compliant.

- Nirsevimab is a human immunoglobulin G1 kappa monoclonal antibody that binds the pre-fusion conformation of the RSV F-protein. *In vitro*, nirsevimab bound the pre-fusion conformation of the RSV F-protein and neutralised strain A and B, RSV with an $IC_{50} \leq 2$ ng/mL. *In vivo*, in the cotton rat model of RSV, the nirsevimab surrogate (IG7) demonstrated EC_{50} and EC_{90} values of 2.9 and 6.8 µg/mL and 1.8 and 5.8 µg/mL, respectively at equivalent clinical dose; therefore, supporting the proposed clinical indication. No evidence of enhancement of RSV infection was observed at any dose evaluated, including sub-efficacious doses in a cotton rat model.

- *In vitro* studies revealed variants with mutations at positions 68, 201 and 208 in the RSV binding site are resistant to nirsevimab. While naturally occurring mutations at these sites have not been observed in a clinical setting, viral resistance will need to be monitored clinically. Amino acid modification in nirsevimab development did not have any effect on effector function.

- No off-target sites were identified in a panel of human tissues (including a range of juvenile, neonate and fetal tissues).

- Examination of safety pharmacology (incorporated into general repeat-dose toxicity study) revealed no effects of nirsevimab on CNS or respiratory function, or on ECG in monkeys.

- The pharmacokinetics of nirsevimab in monkeys and human subjects was generally consistent with the protein nature of the drug, *i.e.*, long half-lives and comparable distribution with reference products.

- Nirsevimab had a low order of acute IV toxicity in monkeys.

- A Repeat-dose toxicity study using the IV and IM routes were conducted in cynomolgus monkeys up to 5 weeks (25-week recovery). The study was adequately conducted yielding high exposure margins. No target organs for toxicity were identified. Nirsevimab was generally well tolerated.

- No genotoxicity studies were conducted. Given the protein nature of the drug, this is considered acceptable. No carcinogenicity studies were conducted. No proliferative lesions were seen in the repeat-dose toxicity study.

- No reproductive and development studies were conducted, which is reasonable given the paediatric indication. No histopathological findings were associated with gonadal tissues.

CONCLUSIONS AND RECOMMENDATION

- Pharmacology studies suggest efficacy against RSV A and B
- The potential risk of treatment failure due to the development of viral variants that are resistant to nirsevimab would need to be monitored clinically.
- Nirsevimab was well tolerated in monkeys.
- There are no nonclinical objections to registration.
- The draft Product Information should be amended as directed on pages 12–13.

ASSESSMENT

AstraZeneca Pty Ltd has applied to register a new biological entity, nirsevimab (BEYFORTUS) against respiratory syncytial virus (RSV) subtype A and B. BEYFORTUS IS indicated for the treatment of lower respiratory tract disease in infants and children. For infants in their first RSV season the recommended dose is 50 mg for < 5 kg b.w. and 100 mg for > 5 kg b.w., and 200 mg for children who remain vulnerable to severe RSV disease entering their second RSV season (administered as 2 x intramuscular injections of 100 mg). A single dose of nirsevimab, administered prior to the start of the RSV season, or from birth for infants born during the RSV season, provides protection for at least 5 months.

General comments

The nonclinical dossier was of good overall quality, and in general accordance with the relevant TGA-adopted guideline (ICH S6[R1][1]). All pivotal safety-related studies were conducted according to GLP.

Nirsevimab belongs to the same pharmacological class as palivizumab, approved by the TGA for similar indications as sought here in 2015 (SYNAGIS)[2].

Pharmacology

Primary pharmacology

Rational and Mechanism of action

Nirsevimab (also known as MEDI8897) is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) that binds the pre-fusion conformation of the respiratory syncytial virus (RSV) F-protein. Nirsevimab is derived from the human monoclonal antibody D25, which locks RSV-F in its pre-fusion state by binding to a quaternary epitope spanning two protomers at the apex of the pre-fusion F trimer (McLellan *et al.*, 2013). A conformational change of the RSV F-protein from pre-fusion state mediates fusion of the viral membrane with a host-cell membrane. The RSV F-protein is thus, a key component of RSV infection (Gilman *et al.*, 2019).

D25 was affinity optimised *in vitro* to generate 1G7, and nirsevimab differs from 1G7 by three amino acid substitutions (termed YTE) in the heavy chain CH2 fragment crystallizable (Fc) region of the mAb, designed to prolong the terminal half-life of the antibody in humans (Griffin *et al.*, 2017 and Robbie *et al.*, 2013). It is proposed the YTE modification increases terminal half-life by increasing FcRn binding affinity at pH 6.0 (Robbie *et al.*, 2013). This prevents degradation and increases recirculation to the surface of the cell, thereby prolonging the serum half-life of the antibody (Dall'Acqua et al., 2006). Nirsevimab has a cynomolgus monkey and human FcRn receptor binding affinity of 253 nM and 161 nM, respectively. In contrast, the YTE substitutions have been reported to reduce the antibody exposure in rodents (Dall'Acqua *et al.*, 2002). Nirsevimab has similar neutralization EC_{50} values for RSV subtypes A and B strains.

Currently, there is no approved RSV vaccine for children. Palivizumab (SYNAGIS)[2] has only been approved for RSV prophylaxis in infants who are at the highest risk for severe RSV disease (*i.e.*, premature infants ≤35 weeks gestational age, children with chronic lung disease of prematurity or children with hemodynamically significant congenital heart disease). With a half-life of approximately one month, palivizumab has to be administered monthly (intramuscular [IM] injection) throughout the RSV season. Hence, the proposed treatment was developed to address the unmet medical need for RSV prevention in otherwise healthy children as a single IM injection to last

[1] ICH S6(R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

[2] Palivizumab (SYNAGIS), ARTG: 231139

a 5-month period.

In vitro

Binding site characterisation

Antibody competition studies revealed that nirsevimab, 1G7, and D25 bind the same region within antigenic site, and the binding site is not shared with other anti-RSV F mAbs, including palivizumab. Crystallographic analysis of nirsevimab revealed discontinuous binding site on RSV F with contact residues in both the F1 and F2 subunits in contact with the heavy or light chains of nirsevimab via hydrogen bonds or salt bridges, as well as amino acids adjacent to a direct contact residue that were within a 5Å radius of the heavy or light chains of the nirsevimab Fab fragment. The sequence conservation at all binding site residues was ≥ 96% based on multiple clinical isolates of RSV A and B isolates. To this end, with the exception of the sites identified in the MARM studies, polymorphic variations in the nirsevimab-binding site revealed no (RSV A) or minimal to moderate (RSV B) effects (4- to 36-fold increase in IC_{50} *cf.* parental strain) on nirsevimab/1G7 susceptibility. The increase in RSV B IC_{50} was associated with polymorphisms in F protein at position 65 alone or in combination at position 211 (K65Q, K65T, and K65Q/S211Q). Interestingly, polymorphic substitution K65Q in combination with substitution K68N or L203I lead to >1000-fold or >3000-fold increases in IC_{50} *cf.* the parental strain.

In vitro neutralisationIn vitro microneutralisation assays with RSV strains A and B demonstrated comparable IC_{50} values for 1G7 and nirsevimab (≤ 2 ng/mL for both strains). Similar average IC_{50} values were reported with 1G7 when tested with multiple clinical isolates of RSV A and B (≤ 3.15 ng/mL), recombinant viruses containing amino acid substitutions around the parental antibody D25 epitope (≤ 12.4 ng/mL), and palivizumab-resistant viruses (≤ 3.2 ng/mL).

In vitro resistance

Serial passing of RSV A2 and RSV B3920 in 250 ng/mL of nirsevimab resulted in MAb-resistant mutants (MARMs) with substitutions in residues 68, 201, and 208 in the nirsevimab binding site leading to lower binding affinity. The substitutions resulted in RSV A resistant variants with 475-fold higher IC_{50} with nirsevimab, and RSV B resistant variants with 5532- to >250000-fold greater IC_{50}. Naturally occurring mutations at these sites have not been observed in a clinical setting (see Section 4.3, Module 2.7.2).

Effector function

While nirsevimab demonstrated *in vitro* binding to immobilized human FcγR's (FcγRI, FcγRIIA, FcγRIIB, and FcγRIII; K_D 8.94 x 10^{-9}, 1.87 x 10^{-5}, 5.30 x 10^{-4}, and 1.67 x 10^{-5} M, respectively), *in vivo* studies conducted with 1G7-TM[3] in cotton rats infected with RSV revealed no difference in anti-viral activity between 1G7 or 1G7-TM. This suggests protection from RSV infection is mediated through neutralization. activity as opposed to Fc-mediated effector function.

In addition to neutralisation, the Fc domain of RSV F-protein–bound IgG can facilitate effector functions that enhance protection against viral infections. Nirsevimab-related antibody-dependent cellular phagocytosis (ADCP), antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement deposition (ADCD), antibody-dependent NK cell activation (ADNKA), and antibody-dependent cellular cytotoxicity (ADCC) activity was demonstrated *in vitro* at clinically relevant concentrations of >0.12 µg/mL, and at levels comparable to that of palivizumab.

In vivo

In vivo studies in cotton rat model infected with RSV A and B variants demonstrated 1G7 EC_{50} and

[3] 1G7-TM – modified 1G7 for reduced FcR binding

EC_{90} values of 2.9 and 6.8 µg /mL and 1.8 and 5.8 µg /mL, respectively, when 0.125 mg/kg to 3 mg/kg was injected intramuscularly one day prior to RSV infection. 1G7 was 11-fold and 9-fold more potent *cf.* palivizumab at decreasing pulmonary viral loads in RSV A- and RSV B-challenged cotton rats, respectively. Since equipotency was demonstrated between 1G7 and nirsevimab, *in vitro*, comparable *in vivo* efficacy for nirsevimab can be reasonably assumed. Furthermore, 1G7 treatment of cotton rats did not attenuate subsequent immune responses to RSV, suggesting 1G7 does not interfere with the development of an immune response to RSV infection, despite significantly reducing the viral load. Thus, based on body surface area estimates, 1G7 appears to demonstrate efficacy at equivalent clinical doses[4]. No evidence of enhancement of RSV infection was observed at any dose evaluated, including sub-efficacious doses.

Secondary pharmacodynamics and cross-reactivity

No dedicated secondary pharmacodynamic studies were conducted. This is consistent with the current guidelines for a product of this nature[1]. Furthermore, nirsevimab is directed against a viral target that is not endogenously expressed in healthy animal or human tissues. Therefore, no cross-reactivity is anticipated. To this end, in two cross-reactivity studies, nirsevimab did not show binding to human tissue based on a panel of 36 different adult human organ/tissue samples and selected juvenile, neonatal, and fetal human tissues as specified by the relevant guidelines[5].

Safety pharmacology

No stand-alone safety pharmacology studies were conducted with nirsevimab, consistent with the relevant guidelines[1]. However, safety pharmacology of nirsevimab was assessed as a component of the one month repeat dose toxicologic study in monkeys. No test-article related cardiovascular risks were observed at doses up to 280-fold the clinical dose based on C_{max}. Furthermore, no respiratory or CNS function effects were noted in the toxicity study.

Pharmacokinetics

No specific studies on metabolism, excretion or pharmacokinetic interactions were conducted. This is in accordance with ICH S6(R1). Since nirsevimab is an IgG monoclonal antibody, the distribution, metabolism and excretion profiles are likely to be similar to that of other mAbs (Ovacik and Lin, 2018).

Pharmacokinetics of nirsevimab was examined in monkey following IV (2 doses) and IM (one dose) administration. Following IV or IM administration, nirsevimab demonstrated no gender differences. The pharmacokinetics of nirsevimab was not influenced by ADAs during the treatment period. However, four (of 12) animals in the high dose IV and IM groups tested positive for ADA during the recovery phase, with variable impact on exposures. The half-life following 5 repeat IV or IM administrations to was approximately 40 days, which was up to 2-fold faster *cf*. human values.

Following IV administration in monkey, nirsevimab exhibited linear and dose proportional TKs after the first IV dose, but exposure increased in slightly less than dose proportional manner after the last weekly dose on Day 29. A similar linearity was also observed in infant and adult exposure in humans. T_{max} in infants and adults was approximately 3-fold longer in humans *cf*. monkey and is consistent with the intended function of the YTE modification.

In comparison to two other anti-RSV F mAbs, MEDI-557 (YTE modified motavizumab) and MEDI-524 (motavizumab), the mean concentration of nirsevimab in bronchoalveolar lavage (BAL), and nasal

[4] Based on EC_{50} and EC_{90} relative to clinical C_{max} values.

[5] EMA/CHMP/BWP/532517/2008 — Guideline on development, production, characterisation and specification for monoclonal antibodies and related products.

wash (NW) was mostly within samples 2-fold to 7-fold of the comparators at equivalent doses.

From a pharmacokinetic perspective, monkeys are considered an acceptable animal model for toxicity studies.

Toxicity

Acute toxicity

No single-dose toxicity studies were performed. This is acceptable, with relevant information on acute toxicity available from repeat-dose toxicity studies instead. No acute toxic effects were apparent in monkeys up to the highest doses tested (50 mg/kg IV and 300 mg/kg IV and IM).

Repeat-dose toxicity

Nirsevimab is proposed as a single dose, administered once, seasonally. However, a repeat dose toxicity study was conducted in monkey with clinical route and a once weekly dosing regimen for a total of 5 weeks, and a 25-week recovery period. Nirsevimab does not have any pharmacological targets in monkey (or in humans). However, nirsevimab has comparable FcRn receptor binding affinity between cynomolgus monkey and human. The use of a single species, and the duration of the study and its design and conduct (including in terms of group size, dose selection and the range of endpoints examined) was appropriate and consistent with relevant TGA-adopted guidelines (ICH S6 [R1] and the EMA guideline on repeated dose toxicity [CPMP/SWP/1042/99 Rev 1 Corr]). The PK parameters were broadly comparable between the two species and was not affected by ADA formation during the dosing period.

Relative exposure

Exposure ratios have been calculated based on animal:human plasma C_{max} and AUC values. Human reference values are from population PK modelling. The AUC data used for animals are the mean of male and female values on the last sampling occasion. Toxicokinetic data for the dosing period was not affected or compromised by ADA formation

Table I. Mean Exposure and Safety Margins of Nirsevimab at the NOAEL in the 1-month Repeat Dose IV/IM Toxicity Study in Cynomolgus Monkeys and in Human Infants and Adults (From Table 3, Toxicology written summary; module 2.6.6)

Cynomolgus monkey				Human					
300 mg/kg/week IV NOAEL		300 mg/week IM NOAEL		Infants (IM 50 mg <5kg, 100 mg ≥5kg)[a, b]		Children - 2nd Season (200 mg)[c, d]		Adults (3000 mg IV)[b]	
$C_{max,5}$ (µg/mL) [SD]	AUC_{1-31} (µg day/mL) [SD]	$C_{max,5}$ (µg/mL) [SD]	AUC_{1-31} (µg day/mL) [SD]	C_{max} (µg/mL) [SD]	AUC_{0-365} (µg day/mL) [SD]	C_{max} (µg/mL) [SD]	AUC_{0-365} (µg day/mL) [SD]	C_{max} (µg/mL) [SD]	AUC_{0-365} (µg day/mL) [SD]
13360 [2704]	208500 [43270]	4,982 [863.4]	92380 [9428]	120 [28.0]	12200 [3,550]	194 [42.2]	21500 [5,520]	1090 [163]	53900 [19,800]
Safety Margins (IV/IM)				111/42	17/8	69/26	10/4	12/5	4/2

$AUC_{(1-31)}$ = cumulative area under the curve from Day 1 to Day 31; $C_{max,5}$ = maximum observed concentration after fifth dose on Day 29; IM = intramuscular; IV

= intravenous; SD = standard deviation

[a] Dose of 50 mg for infants weighing <5 kg and 100 mg for those weighing ≥5 kg entering their first RSV season

[b] Modelling and Simulation Report: Population PK and Exposure-Response Modelling of Nirsevimab in Term and Preterm Children, and Extrapolation to High-Risk Children, 2021

[c] Modelling and Simulation Report: Population PK Modelling of Nirsevimab in Term and Preterm Children, and Extrapolation to Higher-Risk Children, 2022

[d] For children at higher risk of severe RSV disease entering their second RSV season, the recommended dose is 200 mg given as 2 IM injections (2 x 100 mg).

Major toxicities

No major toxicities were identified.

With the exception of elevated globulin, and hypertrophy/hyperplasia of the spleen at 300 mg/kg (IV and IM), no other effects were observed. The elevated globulin was not associated with effects on other clinical pathology or microscopic endpoints. The spleen hypertrophy/hyperplasia is commonly seen with the administration of foreign proteins to monkeys and was potentially attributed to clearance of antibodies from circulation, which is reasonable.

Genotoxicity

No genotoxicity studies were conducted. Given the protein nature of the drug this is considered acceptable in accordance with ICH S6(R1).

Carcinogenicity

Carcinogenicity studies were not conducted; this is acceptable under ICH S6(R1). A repeat-dose toxicity study showed no propensity for proliferative lesions, and the intended target of nirsevimab is of viral origin.

Reproductive and developmental toxicity

No reproductive toxicity studies were submitted. Reproductive organs were unaffected in the repeat-dose toxicity studies. Effects on fertility are not expected given that nirsevimab binds to a viral-specific target that is not expressed in nonclinical models or in humans. Nirsevimab is also only intended for a paediatric population.

Pregnancy classification

No pregnancy classification was assigned given that the product is administered to patients of non-childbearing age.

Local tolerance

No dedicated local tolerance studies were conducted. In the repeat dose toxicity study in monkey, intramuscularly administered nirsevimab, at 100 mg/mL (equivalent to clinical strength), did not result in local irritation.

Paediatric use

Nirsevimab is proposed for paediatric use; however, no specific studies in juvenile animals were submitted. To this end, the Sponsor noted that nirsevimab was evaluated in young cynomolgus monkeys (3.1 to 4.2 years old) in the month repeat-dose study, which did not highlight any toxicology concerns. Nirsevimab is also indicated for infants, an age group not represented in the repeat dose toxicity study. However, cross-reactivity studies conducted with juvenile, neonate and fetal human tissue did not indicate any cross-reactivity. Thus, taken together the absence of an age-matched infant group in the toxicology study is acceptable.

Comments on the Nonclinical Safety Specification of the Risk Management Plan

Key safety concerns arising from nonclinical data are adequately identified in the Safety Specification of the Risk Management Plan (Module 1.8.2).

PRODUCT INFORMATION

ROUND 1 EVALUATION — MILESTONE 5

The following comments refer to the draft Product Information document accompanying the sponsor's letter of application dated 28th October 2022. Where changes are suggested, text proposed to be inserted is underlined and text to be deleted is shown struck-through.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Statements relating to *in vitro* studies interactions with other medicines is acceptable as indicated:

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

Nirsevimab-mediated drug-drug interactions are unlikely as the target of nirsevimab is an exogenous virus."

4.6 FERTILITY, PREGNANCY AND LACTATION

The statements pertaining to Fertility, Pregnancy and Lactation should be amended as indicated.

Effects on fertility

"[6]~~Not applicable~~. Reproductive toxicity studies have not been performed."

Use in pregnancy

The sponsor did not propose a Pregnancy Category. However, a category of B2 is recommended:

"[6]~~Not applicable~~. BEYFORTUS is not indicated for adult usage and animal reproduction studies have not been conducted."

Use in lactation

"[6]~~Not applicable~~. No data available."

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The statements on the mechanism of action and potency are supported by nonclinical data:

"Nirsevimab is a recombinant neutralising human IgG1κ long-acting monoclonal antibody 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 K_D = 0.12 nM and K_D = 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.

The potential for rapid protection was evaluated in a cotton rat model of RSV infection using a non-YTE version of nirsevimab (IG7). Intramuscular administration 1 day prior to inoculation with RSV A or B provided complete protection from viral replication in the upper and lower respiratory tracts."

5.2 PHARMACOKINETIC PROPERTIES

The statement pertaining to pharmacokinetic properties is acceptable.

5.3 PRECLINICAL SAFETY DATA

The statements pertaining to genotoxicity and carcinogenicity are satisfactory as indicated below

Genotoxicity

"Nirsevimab is a monoclonal antibody, as such genotoxicity studies have not been conducted. As a large protein molecule, nirsevimab is not expected to interact directly with DNA or other chromosomal material."

Carcinogenicity

"No carcinogenicity studies have been conducted because nirsevimab binds a viral-specific target that is not expressed in nonclinical models or in humans."

MAIN BODY OF REPORT

1. INTRODUCTION

1.1. BACKGROUND

AstraZeneca Pty Ltd has applied to register a new biological entity, nirsevimab (BEYFORTUS) against respiratory syncytial virus (RSV) subtype A and B. BEYFORTUS IS indicated for the treatment of lower respiratory tract disease in infants and children. For infants in their first RSV season the recommended dose is 50 mg for < 5 kg b.w. and 100 mg for > 5 kg b.w., and 200 mg for children who remain vulnerable to severe RSV disease entering their second RSV season (administered as 2 x intramuscular injections of 100 mg). A single dose of nirsevimab, administered prior to the start of the RSV season, or from birth for infants born during the RSV season, provides protection for at least 5 months.

1.2. RELATIONSHIP TO OTHER DRUGS

Nirsevimab belongs to a single-dose long-acting antibody directed against the pre-fusion conformation of the RSV fusion protein. A similar product, palivizumab, has previously been approved in Australia that targets the fusion protein of RSV (SYNAGIS, ARTG: 231139); however, it is restricted to infants at higher risk for morbidity and mortality from RSV, *i.e.*, premature infants ≤35 weeks gestational age, children with chronic lung disease of prematurity or children with hemodynamically significant congenital heart disease.

1.3. CHEMISTRY AND FORMULATION

Nirsevimab (CAS Number: 1989556-22-0) is a human IgG1 κ monoclonal antibody with a YTE amino acid substitution s47 [redacted] in the Fc domain. The antibody was isolated directly from human B-cells and consists of two heavy chains s47 [redacted] and two light chains s47 [redacted] with a total molecular mass of approximately 150 kDa s47 [redacted] [6]. The laboratory code used for nirsevimab is MEDI8897.

s47 [redacted]

s47 [redacted]

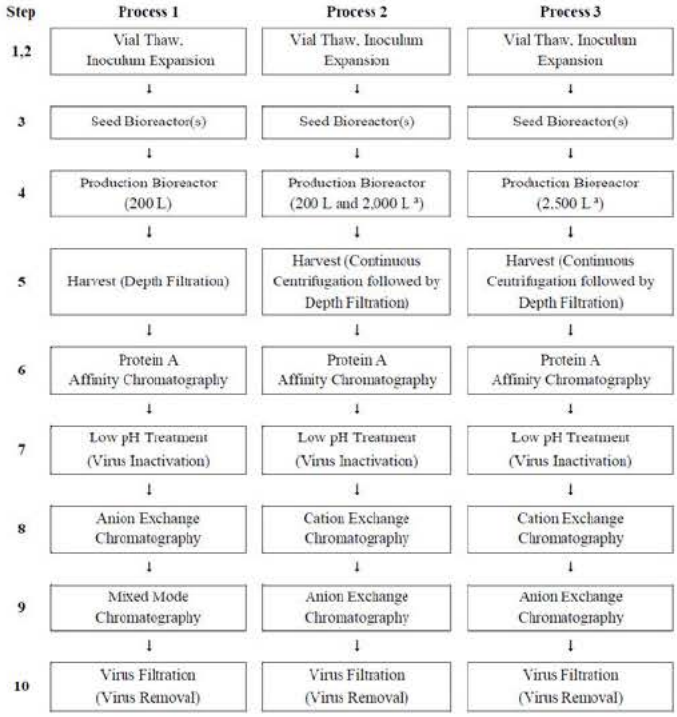
Table 1.1. Product formulation

Ingredient	Purpose	Unit Formula (mg)		Concentration
		(50 mg strength)[a]	(100 mg strength)[b]	
Nirsevimab	s47			
L-Histidine				
L-Histidine hydrochloride monohydrate				
L-Arginine hydrochloride				
Sucrose				
Polysorbate 80				
Water for Injection (WFI)				

s47

1.4. BATCHES USED IN MODULE 4 STUDIES

In vivo pharmacology studies for nirsevimab were conduced with 1G7, as the YTE substitution in nirsevimab results in lower antibody exposure in rodents. The repeat dose toxicity study was conducted with a Process 1 batch of nirsevimab, which was also used in clinical trials D5290C00001 and D5290C00002. The Process 3 product, proposed for clinical application, was manufactured in a different facility and larger scale *cf.* Process 1 nirsevimab. A comparison of the different processes are demonstrated in the following figure:



1.5. OVERSEAS REGULATORY STATUS

A similar application has been approved made in the EU (October 2022) and in the USA (June 2023).

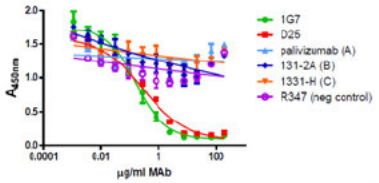
2. PRIMARY PHARMACOLOGY

Nirsevimab was derived from the human monoclonal antibody D25 isolated directly from human B cells (McLellan *et al.*, 2013). Through affinity optimisation and amino acid substitutions in the heavy chain, nirsevimab was designed to bind to the pre-fusion conformation of the RSV F-protein. Thus, nirsevimab does not target native human cell/tissue antigens. The YTE substitutions were added to prolong the terminal half-life of nirsevimab in humans.

A total of 12 pharmacology studies were performed to characterise mechanism of action, *in vitro* and *in vivo* antiviral activity, and *in vitro* antiviral resistance.

2.1. *IN VITRO* STUDIES

Table 2.1. Summary of *in vitro* studies

Study	Assay/Study details	Major findings
Binding site characterisation		
ID8897-0008	Competitive bindings assays (biotinylated-absorbance assays) Test article – biotinylated 1G7, mouse MAbs directed against each of the previously characterised RSV F MAb binding sites (site A: palivizumab; site B: 131-2A; site C: 1331H), HEp-2 cell lin	• None of the competitor MAbs interfered with the binding of biotinylated 1G7 to RSV-infected HEp-2 cells  • **Figure 2.1Different concentrations of competitor MAbs were incubated with RSV-infected HEp-2 cells in the presence of biotinylated 1G7. Binding of biotinylated 1G7 was quantified by measuring absorbance at 450 nm after incubation with streptavidin-HRP and an ABTS substrate (Source – Figure 8-2 from ID8897-0008 study report)**
ID8897-0010	Crystallographic analysis of nirsevimab Fab complexed with RSV A2 and RSV B 9320 fusions proteins to define nirsevimab binding site and contact residues	• The analysis revealed discontinuous binding site on RSV F with contact residues in both the F1 and F2 subunits • The binding site(s) included the F amino acids directly in contact with the heavy or light chains of nirsevimab via hydrogen bonds or salt bridges, as well as amino acids adjacent to a direct contact residue that were within a 5Å radius of the heavy or light chains of the nirsevimab Fab fragment • The majority of amino acids in the binding site (24 of 25 positions in RSV A and 23 of 25 positions in RSV B) exhibited >99% sequence conservation against 1278 of RSV A and 610 of RSV B clinical isolates • Sequence conservation at all binding site residues was ≥ 96%.
ID8897-0005	Surface Plasma Resonance (SPR) based K_D determination of nirsevimab for human and cynomolgus monkey FcRn	• Human K_D 161 nM • Monkey K_D 253 nM
In vitro neutralisation		

Study	Assay/Study details	Major findings
ID8897-0001	Microneutralisation assays with RSV strain A and B in HEp-2 cell line Test articles: nirsevimab, 1G7 (parent, no YTE substitution) and palivizumab (commercial comparator)	• Nirsevimab IC_{50} - 1.6 and 1.8 ng/mL against RSV A2 and RSV B9320 • 1G7 IC_{50} - 1.7 and 2.1 ng/mL against RSV A2 and RSV B9320 • Palivizumab IC_{50} - 347 and 242 ng/mL against RSV A2 and RSV B9320
ID8897-0002	Microneutralisation assays with 54 RSV strain A and 41 strain B clinical isolates in HEp-2 cell line, recombinant viruses containing amino acid substitutions around the parental antibody, D25, epitope, and palivizumab-resistant viruses Test article: 1G7	• 1G7 IC_{50}: o RSV A and B clinical isolates, respectively - 3.15 ng/mL (range 0.48 to 15 ng/mL) and 3.0 ng/mL (range 0.8 to 59.7 ng/mL) o Recombinant variants - 1.1 to 12.4 ng/mL o Palivizumab-resistant viruses 0.44 to 3.2 ng/mL
ID8897-0003-amend-1	*In vitro* microneutralisation assays with MAb-resistant mutants (MARMs) generated using serial passage of RSV A2 or RSV B9320 in the presence of nirsevimab	• RSV A resistant variants: N208Y single amino acid substitution in the F1 epitope region of RSV A F protein (6 variants) • RSV B9320 resistant variants: single amino acid substitution at 208 (N208D or N208S); double substitutions at 68 f (K68N) in combination with another change either at position 201 (K68N/N201S) or 208 (K68N/N208S) • RSV A resistant variants showed 475-fold higher IC_{50} *cf.* parent/non-resistant variant • RSV B resistant variants showed 5532-fold to >250000-fold greater IC_{50} *cf.* parent/non-resistant variant, depending on type of substitution
Invito reistance		
ID8897-0011-amend-1	*In vitro* microneutralisation assays with RSA polymorphic variants (from clinical isolates) in nirsevimab binding site and identification of nirsevimab-resistant variants	• All RSV A and the majority of RSV B amino acid polymorphisms in the nirsevimab-binding site had no effect on nirsevimab/1G7 susceptibility (IC_{50} values comparable to parental viruses and contemporary RSV clinical isolates) • RSV B variants with polymorphisms in F protein at position 65 alone or in combination at position 211 (K65Q, K65T, and K65Q/S211Q) returned nirsevimab IC_{50} values approx. 4- to 36-fold higher *cf.* the parental strain • Polymorphic substitution K65Q in combination with substitution K68N or L203I lead to >1000-fold or >3000-fold increases in IC50 values *cf.* the parental strain
Effector function		
ID8897-0031	Fc receptor binding affinity (nirsevimab) and comparative activity (nirsevimab, 1G7 and 1G7-TM (reduced effector function)) using SPR and microneutralisation assays Fc effector function assay: Cotton rats infected with RSA A2. Test articles 1G7 and 1G7-TM at 2.0, 1.0, or 0.5 mg/kg	• Nirsevimab Fc binding: o K_D for FcγRI, FcγRIIA, FcγRIIB, or FcγRIII A158V were 8.94×10^{-9}, 1.87×10^{-5}, 5.30×10^{-4}, and 1.67×10^{-5} M, respectively • Microneutralisation assays IC_{50} values: o Nirsevimab - 2.2 ng/mL o 1G7 - 2.0 ng/mL o 1G7-TM - 2.0 ng/mL • Fc effector function (1G7 or 1G7-TM only) o 1G7 or 1G7-TM resulted in comparable dose-dependent reduction in RSV replication in the lungs and nasal turbinates NT

Study	Assay/Study details	Major findings
ID8897-0033 Amend 1	Nirsevimab Fc-Mediated effector function characterisation; antibody-dependent cellular phagocytosis (ADCP), antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement deposition (ADCD), and antibody-dependent NK cell activation (ADNKA), and antibody-dependent cellular cytotoxicity (ADCC) in THP-1 macrophage cell line Test articles: nirsevimab, palivizumab and R347 (negative control)	• Nirsevimab-mediated ADCP and ADCD was comparable to that of palivizumab • Nirsevimab-mediated ADNP, ADNKA and ADCC was comparable to that of palivizumab; however, the levels of ADNP, ADNKA and ADCC was not statistically significant *cf.* negative control • The absence of statistical significance in ADNP, ADNK and ADCC assays were attributed to potential donor-to-donor variability

2.2. *IN VIVO* STUDIES

Study	Study details	Major findings
MEDI8897-0006	Antiviral activity - cotton rat model of RSV A2 Test articles: 1G7 (0.125 mg/kg to 3 mg/kg IM) and palivizumab (0.25 mg/kg to 8 mg/kg) one day prior to RSV challenge	• 1G7 EC_{50} and EC_{90} 2.9 and 6.8 µg /mL, respectively • Palivizumab EC_{50} and EC_{90} 18.7 and 76.4 µg /mL, respectively
ID8897-0007	Antiviral activity - cotton rat model of RSV B Test articles: 1G7 (0.3125 mg/kg to 1.5 mg/kg IM) and palivizumab (0.25 mg/kg to 8 mg/kg) one day prior to RSV challenge	• 1G7 EC_{50} and EC_{90} 1.8 and 5.8 µg /mL, respectively • Palivizumab EC_{50} and EC_{90} 6.9 and 51.4 µg /mL, respectively
ID8897-0032	1G7 effect on RSV A2 immunogenicity – cotton rat model Test articles: 1G7, R347 and PBS	• IM injection of 1G7 1-day prior to RSV A2 infection provided complete protection from viral replication in the upper and lower respiratory tracts. • Animals were still capable of mounting an anti-RSV antibody response 77-days later despite 1G7 attenuating viral replication No evidence of ADE of infection was observed at sub-efficacious doses

3. SECONDARY PHARMACODYNAMICS

No secondary pharmacodynamic studies were conducted since nirsevimab is directed against a viral target that is not endogenously expressed in healthy animal or human tissue. However, two tissue cross-reactivity studies were conducted using human adult, juvenile and fetal tissue panel.

Table 3.1. Summary of secondary pharmacodynamic and cross-reactivity studies

Study; assay details	Major findings
20046491; Tissue cross reactivity with immunohistochemical analysis Tissues: adrenal, heart, salivary gland, bladder (urinary), kidney (glomerulus, tubule), skin, blood cells, liver, spinal cord, blood vessels (endothelium), lung, spleen, bone marrow, lymph node, striated muscle (skeletal), brain – cerebellum, ovary, testis, brain – cerebral cortex, pancreas, thymus, breast, parathyroid, thyroid, colon (large intestine), peripheral nerve, tonsil, eye, pituitary, ureter, fallopian tube, placenta, uterus – cervix, gastrointestinal (GI) tract, prostate, uterus – endometrium	• No tissue staining detected
20060018; Tissue cross reactivity with immunohistochemical analysis Tissues: Juvenile (Bladder, cerebrum, thymus, uterus), Neonatal (adrenal, oesophagus, eye (pole), heart, intestine, kidney, liver, lung, muscle, pituitary, skin, small intestine, spinal cord, spleen, stomach, testes), fetal tissue (adrenal, bone marrow, blood vessels, brain, oesophagus, eye, heart, kidney, large intestine, liver, lung, mammary, muscle, ovary, pancreas, skin, small intestine, spleen, stomach)	• No tissue staining detected

4. SAFETY PHARMACOLOGY

No stand-alone safety pharmacology studies were conducted with nirsevimab, consistent with the relevant guidelines[1,7]. However, safety pharmacology of nirsevimab was assessed as a component of the one month repeat dose toxicologic study in monkeys. Tested ECG parameters included RR, PR, QT intervals, QRS duration and heart rate. No adverse nirsevimab -related effects following up to 300 mg/kg IV or 300 mg IM once weekly for 5 total doses.

5. PHARMACOKINETICS

5.1. METHODS OF ANALYSIS

Quantification of nirsevimab in the serum of cynomolgus monkeys was by enzyme-linked immunosorbent assay (ELISA). Lower limits of quantification (LLoQ) were 0.50 µg/mL in monkey serum. A non GLP-ELISA assay was used to quantify nirsevimab in cynomolgus monkey nasal wash (quantitative range was 50 to 6400 ng/mL). Electro-chemiluminescence immunoassay was used to quantify anti-nirsevimab antibodies (ADAs) in cynomolgus monkey serum. LLoQ for ADA was 62.5 ng/mL in monkey serum

5.2. ABSORPTION AND SERUM KINETICS

5.2.1. Repeat-dose studies

The toxicokinetic data gathered from the 5-week repeat dose monkey toxicity study are documented in the following table:

[7] CPMP/ICH/539/00 - Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals

Table 5.1. Pharmacokinetic parameters for repeat-dose administration of nirsevimab in monkeys

Study	Dose (mg/kg /day); route; frequency		Day of sampling	C_{max} (µg/mL)	T_{max} (D)	$AUC_{(1d-7d \text{ or } 21d-28d)}$ (µg·d/mL)
				♂/♀ combined	♂/♀ combined	♂/♀ combined
Study 1468-038 [5 weeks] 3 over 0–24 h; $n=3$ or 6	50 (IV)	QW	1	1678	0.104	5909
			29	3772	0.014	5852
	300 (IV)		1	8782	0.021	30040
			29	13360	0.099	19710
	300 (IM)		1	1774	2.333	9334
			29	4982	1.0	8513

Mean half-life ($t_{1/2}$) was 40.45 and 39.91 days, following administration of 300 mg/kg IV and IM, respectively.

5.2.2. Serum kinetics in human subjects

Based on the analysis described in Module 5.3.3.5., the mean pharmacokinetic parameters are shown in the following table.

Table 5.2. Summary of post-hoc predicted PK parameters for the MEDLEY final population PK model

Parameter		D5290C00003 (N=916)	MELODY (N=960)	MEDLEY (N=592)	Total (N=2468)
Clearance at baseline (mL/day)	Mean (SD)	3.39 (1.62)	4.02 (2.02)	3.37 (1.72)	3.63 (1.84)
	Median [Min, Max]	3.05 [1.13, 12.4]	3.60 [0.941, 28.9]	3.05 [1.17, 15.5]	3.28 [0.941, 28.9]
	Geo. mean (Geo. CV%, Geo. SD)	3.05 (48.1%, 1.58)	3.66 (44.0%, 1.52)	3.04 (46.7%, 1.56)	3.27 (47.2%, 1.57)
Total volume at baseline (mL)	Mean (SD)	449 (170)	530 (205)	466 (199)	485 (194)
	Median [Min, Max]	428 [171, 1330]	502 [200, 2450]	440 [199, 2620]	462 [171, 2620]
	Geo. Mean (Geo. CV%, Geo. SD)	418 (39.7%, 1.47)	500 (34.7%, 1.40)	435 (37.3%, 1.43)	452 (38.2%, 1.45)
Predicted terminal half-life (days)	Mean (SD)	67.7 (10.1)	68.7 (10.9)	71.3 (9.24)	68.9 (10.3)
	Median [Min, Max]	67.2 [32.7, 104]	68.9 [28.3, 143]	72.1 [30.3, 105]	69.3 [28.3, 143]
	Geo. Mean (Geo. CV%, Geo. SD)	66.9 (15.5%, 1.17)	67.8 (16.3%, 1.18)	70.7 (14.0%, 1.15)	68.1 (15.6%, 1.17)
Predicted C_{max} (µg/mL)	Mean (SD)	98.0 (35.6)	121 (29.5)	124 (28.2)	113 (33.7)
	Median [Min, Max]	90.3 [29.9, 211]	120 [32.5, 198]	124 [23.9, 198]	113 [23.9, 211]
	Geo. mean (Geo. CV%, Geo. SD)	91.9 (37.3%, 1.43)	118 (26.5%, 1.30)	120 (26.0%, 1.29)	108 (33.4%, 1.38)
Predicted AUC_{0-365} (day•mg/mL)	Mean (SD)	9.15 (2.68)	12.4 (3.72)	12.5 (3.48)	11.2 (3.68)
	Median [Min, Max]	8.90 [2.93, 18.0]	12.0 [2.66, 25.6]	12.2 [2.41, 22.4]	10.8 [2.41, 25.6]
	Geo. Mean (Geo. CV%, Geo. SD)	8.76 (31.0%, 1.35)	11.9 (31.9%, 1.37)	12.0 (30.4%, 1.35)	10.6 (34.9%, 1.40)
$AUC_{baseline\ CL}$ (day•mg/mL)	Mean (SD)	18.1 (8.15)	21.7 (6.83)	23.3 (6.59)	20.8 (7.59)
	Median [Min, Max]	16.4 [4.02, 44.4]	20.9 [3.46, 53.2]	23.4 [4.10, 42.7]	20.1 [3.46, 53.1]
	Geo. mean (Geo. CV%, Geo. SD)	16.4 (48.1%, 1.58)	20.6 (33.7%, 1.39)	22.3 (32.1%, 1.37)	19.3 (41.5%, 1.49)

Source: ASTR-NIRSE-run-plots.R (run224)
Note: 16 samples with |CWRES|>5 were removed in the MEDLEY final model.

Table 5.3. Summary of post-hoc predicted PK parameters for adult subjects for the MEDLEY final population PK model

Parameter		300 mg IV (N=6)	300 mg IM (N=78)	3000 mg IV (N=6)
Clearance at baseline (mL/day)	Mean (SD)	48.1 (7.47)	56.2 (21.5)	72.6 (59.9)
	Median [Min, Max]	51.1 [34.0, 53.2]	51.6 [26.1, 140]	50.4 [41.6, 195]
	Geo. mean (Geo. CV%, Geo. SD)	47.5 (17.5%, 1.19)	53.0 (34.3%, 1.40)	60.6 (63.2%, 1.79)
Total volume at baseline (mL)	Mean (SD)	5870 (892)	5940 (1300)	5460 (953)
	Median [Min, Max]	6130 [4280, 6830]	5750 [3520, 9270]	5220 [4450, 7260]
	Geo. Mean (Geo. CV%, Geo. SD)	5810 (16.7%, 1.18)	5800 (22.2%, 1.25)	5400 (16.4%, 1.18)
Predicted terminal half-life (days)	Mean (SD)	86.2 (9.07)	79.2 (17.6)	69.5 (25.5)
	Median [Min, Max]	83.1 [78.5, 103]	82.0 [36.9, 124]	76.0 [21.1, 96.5]
	Geo. Mean (Geo. CV%, Geo. SD)	85.8 (10.0%, 1.10)	77.0 (25.4%, 1.28)	63.2 (59.2%, 1.73)
Predicted C_{max} (µg/mL)	Mean (SD)	96.9 (15.2)	45.0 (12.2)	1090 (163)
	Median [Min, Max]	94.3 [75.5, 121]	42.9 [25.4, 82.9]	1110 [773, 1240]
	Geo. mean (Geo. CV%, Geo. SD)	6.0 (15.8%, 1.17)	43.5 (27.1%, 1.30)	1070 (16.9%, 1.18)
Predicted $AUC_{0\text{-}365}$ (day•mg/mL)	Mean (SD)	6.21 (1.19)	4.93 (1.49)	53.9 (19.8)
	Median [Min, Max]	5.76 [5.51, 8.57]	58.4 [15.5, 70.9]	5.76 [5.51, 8.57]
	Geo. Mean (Geo. CV%, Geo. SD)	6.13 (17.2%, 1.19)	4.70 (33.1%, 1.38)	48.7 (62.1%, 1.77)
$AUC_{baseline\ CL}$ (day•mg/mL)	Mean (SD)	6.39 (1.24)	5.96 (1.86)	54.9 (20.3)
	Median [Min, Max]	5.88 [5.64, 8.83]	5.81 [2.14, 11.5]	59.7 [15.4, 72.1]
	Geo. mean (Geo. CV%, Geo. SD)	6.31 (17.5%, 1.19)	5.66 (34.3%, 1.40)	49.5 (63.2%, 1.79)

Source: ASTR-NIRSE-run-plots.R (run224) Note: 16 samples with |CWRES|>5 were removed in the MEDLEY final model.
Abbreviations: AUC=area under the concentration-time curve; CV=coefficient of variation; CWRES=conditional weighted residuals; Geo.=geometric; Max=maximum; Min=minimum; N=number of subjects with available information; PopPK=population pharmacokinetic; SD=standard deviation

Table 5.4. Summary of post hoc predicted PK parameters for the final pop PK 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_{0-365} (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)

Modelling and Simulation Report Population PK Modelling of Nirsevimab (MEDI8897) in Term and Preterm Children, and Extrapolation to Higher-Risk Children Nirsevimab (MEDI8897)

5.3. DISTRIBUTION, METABOLISM, AND EXCRETION

Since nirsevimab is an IgG monoclonal antibody, the distribution, metabolism and excretion profiles are likely to be similar to that of other mAbs (Ovick and Lin, 2018).

5.3.1. Tissue distribution

No dedicated distribution studies were conducted. However, distribution of nirsevimab benchmarked against MEDI-557 (YTE modified motavizumab) and MEDI-524 (motavizumab), in serum, bronchoalveolar lavage (BAL), and nasal wash (NW) samples in monkeys following a single IV administration are shown in Table 5.1.

Table 5.1. Tissue distribution of nirsevimab, motavizumab and YTE modified motavizumab

Study details	Findings
Study 20089726 Monkey (Cynomolgus; ♂) Test articles: Single IV dose Nirsevimab 50 mg/kg, 150 mg/kg MEDI-524 (motavizumab) 50 mg/kg MEDI-557 (YTE modified motavizumab) 150 mg/kg Analysis - ELISA *n* = 5	• Serum PK for all 3 test articles is indicated in table below. • Nirsevimab serum exposure was higher than for MEDI-524 and MEDI 557 at equivalent doses, respectively • Mean concentration of nirsevimab in BAL samples 72 hours post-dose were within 1- to 2-fold of MEDI-524 and MEDI 557 and the partition ratio (as percent of mean serum concentration) of nirsevimab in BAL was within 2- to 3-fold of the other mAbs • Mean concentration of nirsevimab in NW samples were within 2- to 3-fold of the comparator mAbs at 24 hours and within 2- to 7-fold at 72 hours • High individual variability was reported

Parameters	MEDI-524	MEDI-557	MEDI8897	
Dose (mg/kg)	50	150	50	150
Tmax (day)	0.0208 (0.00)	0.0208 (0.00)	0.0208 (0.00)	0.0208 (0.00)
Cmax (µg/mL)	1100 (134)	4000 (458)	1570 (64.9)	4520 (540)
AUC_{0-3} (day·µg/mL)	1710 (130)	6690 (535)	3100 (167)	9910 (1050)
Dose Normalized AUC_{0-3} ((day·µg/mL)/mg)	10.2 (1.28)	13.9 (1.51)	19.3 (1.37)	19.8 (1.48)

Values are presented as mean, n = 5 (standard deviation)
AUC0-3 = area under the curve from time 0 to 3 days; Cmax = maximum observed concentration;
Tmax = time at which Cmax was observed.

6. SINGLE-DOSE TOXICITY

No single-dose toxicity studies were conducted.

7. EPEAT-DOSE TOXICITY

One repeat dose toxicity study was conducted in cynomolgus monkey.

7.1. MONKEY

7.1.1. 5-week study

Study: 1468-038 **Laboratory:** MPI Research, Inc., 54943 North Main Street, Mattawan, Michigan 49071-8353 **Date:** 03 July 2014 (First dose: Jul 2006) **GLP:** Yes **Lot No.:** 84435.037	**Strain:** Cynomolgus monkey **Age:** ~3.1-4.2 years **Route and frequency:** IV and IM, weekly **Dose:** Group 1: 0 (IV and IM); Group 2: 50 mg/kg IV; Group 3: 300 mg/kg IV; Group 4: 300 mg (fixed IM) **Vehicle:** 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.04% PS80 pH 6.0. **Strength:** 10 mg/mL (50 mg/kg IV), 60 mg/mL (300 mg/kg IV) or 100 mg/mL (300 mg/kg IM) **Group size:** 6/sex, except Group 2 (50 mg/kg IV) 3/sex **Duration:** 5 weeks (25 weeks recovery)
Parameters Evaluated: Mortality, cageside and clinical observations, injection site scoring, body weight; and ophthalmoscopic, physical, and electrocardiographic examinations; and clinical and anatomic pathology. Toxicokinetic assessment was conducted for nirsevimab in blood collected at various timepoints and in nasal wash samples collected prior to necropsy. Immunogenicity was assessed by evaluation of ADA in blood collected pre-dose on Days 1 and 29 (for interim analysis) and every 4 weeks during the recovery phase on Days 57, 85, 113, 141 and 169.	

Study: 1468-038 **Laboratory:** MPI Research, Inc., 54943 North Main Street, Mattawan, Michigan 49071-8353 **Date:** 03 July 2014 (First dose: Jul 2006) **GLP:** Yes **Lot No.:** 84435.037	**Strain:** Cynomolgus monkey **Age:** ~3.1-4.2 years **Route and frequency:** IV and IM, weekly **Dose:** Group 1: 0 (IV and IM); Group 2: 50 mg/kg IV; Group 3: 300 mg/kg IV; Group 4: 300 mg (fixed IM) **Vehicle:** 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.04% PS80 pH 6.0. **Strength:** 10 mg/mL (50 mg/kg IV), 60 mg/mL (300 mg/kg IV) or 100 mg/mL (300 mg/kg IM) **Group size:** 6/sex, except Group 2 (50 mg/kg IV) 3/sex **Duration:** 5 weeks (25 weeks recovery)
Noteworthy Findings: There were no adverse local or systemic effects of MEDI8897. Minor MEDI8897-related findings included minimal increases in globulin (males at 300 mg/kg, IV) that were not associated with effects on other clinical pathology or microscopic endpoints. At the recovery intervals (Days 57-169), globulin values continued to be mildly increased in males receiving 300 mg/kg IV and were also statistically increased in the 300 mg IM group. Microscopic changes in the spleen (red pulp macrophage hypertrophy/hyperplasia) were noted at terminal necropsy. This microscopic finding is commonly seen with the administration of foreign proteins to monkeys and may be related to the clearance of antibodies from circulation.	
Anti-drug Antibodies: Evaluated pre-dose on Days 1 and 29 and every 4 weeks during recovery phase. No animals tested ADA positive during the treatment phase. Four of 18 animals tested ADA positive during the recovery phase with variable impact on TK.	
Toxicokinetics: From 50 mg/kg IV to 300 mg/kg IV, nirsevimab exhibited linear and dose proportional toxicokinetics after the first IV dose, but TK exposure increased in slightly less than dose proportional manner after the last weekly dose on Day 29. No sex differences in TK parameters were noted during treatment period.	
Nasal wash samples: Nasal wash samples collected prior to each necropsy on Days 31 and 169 were evaluated for nirsevimab concentration. On Day 31, the mean partition ratio of nirsevimab nasal concentrations to nirsevimab serum concentrations following 50 mg/kg IV, 300 mg/kg IV, and 300 mg IM was 0.000091, 0.000038, 0.000032, respectively. No quantifiable levels of NIRSEVIMAB were measured in the nasal wash samples in the recovery animals by Day 169.	

8. REPRODUCTIVE AND DEVELOPMENTAL STUDIES

No reproductive toxicity studies were conducted.

8.1. JUVENILE ANIMALS

No dedicated juvenile toxicity studies were conducted. The repeat-dose toxicity studies were however conducted in juvenile monkey ages 3.1 to 4.2 years.

9. LOCAL TOLERANCE

No dedicated local toxicity studies were conducted. However, local tolerance was assessed as a component of the one-month repeat dose toxicity study (1468-038).

Sites of injection (IV and IM) were evaluated for erythema/eschar and oedema changes according to the dermal Draize score pre-dose, approximately 2 to 4 hours post-dose on dosing days and then daily for 4 days

There were no nirsevimab-related signs of local irritation. Any transient and spurious findings of erythema and oedema were comparable between treated and control animals and correlated with microscopic findings of inflammation and haemorrhage at the infusion sites

10. OTHER TOXICITY STUDIES

Two tissue cross-reactivity studies were submitted which have been discussed under secondary pharmacodynamic studies.

10.1. IMMUNOGENICITY

Immunogenicity was examined as part of the 5-week repeat dose toxicity study.

No animals tested ADA positive during the treatment phase. Four of 18 animals tested ADA positive during the recovery phase with variable impact on TK

10.2. IMMUNOTOXICITY

No immunotoxicity studies were conducted.

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Clinical Evaluation Report
Prescription Medicines Authorisation Branch

Active substance: nirsevimab

Product name: Beyfortus™

Sponsor: AstraZeneca Pty Ltd

Submission number: PM-2022-04428-1-2

eSubmission number: e006590

First round evaluator: s22 [redacted]

Date of first round report: 11th April 2023

TRIM reference:

Second round evaluator: s22 [redacted]

Date of second round report: 22nd June 2023

TRIM reference: D23-5482073

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989*, applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

Contents

List of abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
AAP	American Academy of Pediatrics	LAR	Legally Authorized Representative
Ab	Antibody	LLOQ	Lower limit of quantitation
ADA	anti-drug antibody	LRTI	Lower respiratory tract infection
AE	Adverse event	MAA	Marketing Authorisation Application
AESI	adverse event of special interest	MA	Medically attended
AR	Adverse reaction	mAb	Monoclonal antibody
ASA	Australian-Specific Annex	MedDRA	Medical Dictionary for Regulatory Activities
AUC	Area under the serum concentration-time curve	MHRA	Medicines and Healthcare products Regulatory Agency
$AUC_{baseline\ CL}$	Area under the curve baseline clearance	MSD	Meso Scale Discovery
$AUC_{0-\infty}$	Area under the serum concentration-time curve from time zero to infinity	Mth(s)	Month(s)
BPD	Bronchopulmonary dysplasia	nAbs	Neutralising Antibodies against RSV
CF	Cystic fibrosis	NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CHD	Congenital heart disease	nirsevimab	MEDI8897
CHMP	Committee for Medicinal Products for Human Use	NNV	number needed to vaccinate
CHO	Chinese hamster ovary	NOCD	New Onset of Chronic Disease
CI	Confidence Interval	nos.	Number
CL	systemic clearance	OTC	Over the counter
CLD	Chronic lung disease	PBS	pharmaceutical benefits scheme
CL/F	Extravascular systemic clearance	PFS	pre-filled syringe
C_{max}	Maximum serum concentration	PI	Product Information
CMI	Consumer Medicine Information	PIP	Paediatric Investigational Plan
CPK	Creatine Phosphokinase	PK	Pharmacokinetics
conc'n(s)	Concentration(s)	PP	Per-protocol
COVID-19	COVID disease	PPF	Pre-planning pre-submission form
CSR	Clinical Study Report	PopPK	Population PK
DBL	Database lock	PT	Preferred Term
DCO	Data cut-off	QC	Quality control
DEC	Dose Escalation Committee	QPPV	Qualified Person responsible for PharmacoVigilance
ELISA	Enzyme-linked immunosorbent assay	RMP	Risk Management Plan
EM(E)A	European Medicines Agency	RR	Relative risk
ER	Emergency room	RRR	Relative risk reduction
EU	European Union	RSV	Respiratory syncytial virus
F	Bioavailability	SAE	Serious Adverse Event
Fc	Fragment crystallisable	SAP	Statistical Analysis Plan
FDA	Food and Drug Administration	SD	Standard deviation
GA	Gestational age	SmPC	Summary of Product Characteristics
GB	Great Britain	SOC	System Organ Class
GCP	Good Clinical Practice	Subgp	Subgroup
GMFRs	Geometric fold rises	Subpop'n	Sub population
GLP	Good laboratory practice	$t_{1/2}$	Terminal-phase elimination half-life
GMT	Geometric Mean Titre	TGA	Therapeutic Goods Administration
gp	Group	t_{max}	Time to maximum serum concentration
Hb	Haemaglobin	ULOQ	Upper limit of Quantitation
hMPV	Human metapneumovirus	URTI	Upper respiratory tract infection
HRU	Health resource utilisation	US or USA	United States
IC	Immunocompromised	UTI	Urinary tract infection
IC_{50}	conc'n producing 50% inhibition	V_{diss}	Volume of distribution

Abbreviation	Meaning	Abbreviation	Meaning
IP	Investigational Product	Vn.	Version
ICU	Intensive care Unit	vs.	Versus
iCSR	interim Clinical Study Report	V_{ss}	Intravenous steadystate volume of distribution
IgG1κ	human immunoglobulin G1 kappa	V_{ss}/F	Extravascular steady-state volume of distribution
IM	Intramuscular	V_z	Intravenous terminal-phase volume of distribution
ITT	Intention-to-treat	V_z/F	Extravascular terminal-phase volume of distribution
IV	Intravenous	wGA	weeks gestational age
IWRS	Interactive web response system	wk(s)	Week(s)
lab	Laboratory	Yr(s)	Year(s)
		YTE	M252Y/S254T/T256E triple amino acid substitution

List of tables and figures

1. Submission details

1.1. Identifying information

Submission number	**PM-2022-04428-1-2**
eSubmission number	**e006590**
eSubmission sequences covered in this report	**Seq. no: 0001; Rel. Seq. no: 0000**
Sponsor	**AstraZeneca Pty Ltd**
Trade name	**BEYFORTUS™**
Active substance	**nirsevimab**

1.2. Submission type

This is a Type 1 Category A Application for Beyfortus™ (nirsevimab) 100mg/mL (50 mg in 0.5mL and 100mg in 1mL) solution for injection prefilled syringes (PFS) for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in infants and children.

1.3. Drug class and therapeutic indication

Nirsevimab is a recombinant human human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) that has potent neutralising activity against both RSV subtype A and B strains. Nirsevimab has been engineered with a triple amino acid substitution (M252Y/S254T/T256E [YTE]) in the fragment crystallisable (Fc) region to prolong serum half-life. Dosed according to a fixed dose regimen, a single dose aims to provide a minimum of 5 months (mths) protection. Nirsevimab has the potential to address the major medical need because:

- RSV disease usually occurs in predictable annual epidemics, typically lasting <5 mths;
- A single dose of nirsevimab, administered prior to the start of the RSV season, or from birth for infants born during the RSV season, provides protection for at least 5 mths;
- A single dose of nirsevimab offers advantages over the current standard of care (i.e. palivizumab, which requires 5 monthly injections throughout the RSV season) for infants and children at higher risk of severe disease, including those who remain vulnerable to severe RSV disease in their second RSV season;
- Nirsevimab provides rapid protection and therefore allows for a responsive approach to changing seasonality, such as that observed in the COVID disease (COVID-19) pandemic.

At the time of the original submission to the TGA, Nirsevimab was not registered in any region. However, the Applicant in a letter dated 13-Dec-2022, indicated both the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) had approved the BEYFORTUS Marketing Authorisation Application (MAA) in the European Union (EU) and Great Britain (GB) respectively, with both approvals based on the first season data package and associated indication.

Proposed indication, dosing recommendations and product details: The following are the proposed indication and dosing recommendations. BEYFORTUS is indicated for the prevention of RSV lower respiratory tract disease in:

i) Neonates and infants entering or 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, which may include but is not limited to children with: Chronic lung disease of prematurity (CLD); Haemodynamically significant congenital heart disease (CHD); Immunocompromised (IC) states; Down syndrome; Cystic fibrosis (CF); Neuromuscular disease; Congenital airway anomalies.

Infants entering their first RSV season: The recommended dose is a single fixed dose of 50 mg for body weight <5 kg and a single fixed dose of 100 mg for body weight ≥5 kg. BEYFORTUS should be administered from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season. Children who remain vulnerable to severe RSV disease entering their second RSV season – the recommended dose is a single dose of 200 mg (i.e. 2 x 100 mg intramuscular (IM) injections). For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of BEYFORTUS, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.

1.4. Dosage forms and strengths

BEYFORTUS nirsevimab 50 mg in 0.5 mL solution for injection prefilled syringes and BEYFORTUS nirsevimab 100 mg in 1 mL solution for injection prefilled syringes.

1.5. Dosage and administration

BEYFORTUS is a preservative free, sterile, solution for injection presented in a single-dose needleless PFS which is intended for IM injection only. One strength is proposed (100mg/mL nirsevimab) in two presentations - 50mg in 0.5mL and 100mg in 1mL PFS. All excipients have previously been used in other solution for injection products registered in Australia. Both presentations have two pack sizes proposed – 1 PFS and 5 PFS per carton. No package inserts are proposed for supply with the product – instead the most up-to-date Product Information (PI) will be available digitally.

1.6. Proposed changes to the product documentation

Not applicable this is a new drug application.

2. Background

2.1. Information on the condition being treated

In Australia, RSV was made a notifiable disease in July 2021 reflecting the high disease burden and need for routine surveillance data to develop national health policies. As of the 01-Sep-2022, all states have implemented a notification system (National Notifiable Disease List 2022, NSW RSV fact sheet). **Burden of disease:** RSV is the most common cause of lower respiratory tract infection (LRTI) among infants and young children globally and is the major cause of hospital admission, with an estimated 33 million clinical cases and 3.6 million hospitalisations in children <5 years (yrs) of age in 2019 (Li (2022a)). ≈59600 in-hospital deaths are estimated for this age group (gp), with 43600 reported in lower-middle income countries. While the mortality rate due to RSV infection is low in high-income countries, inpatient disease burden is high, with the greatest burden occurring in young infants. It has been estimated that, in the absence of immunisation, there are ≈590000 medically attended RSV (MA RSV) LRTIs annually among US infants (Rainisch). Epidemiological and molecular studies have classified RSV into 2 highly divergent phylogenetic subgroups (subgps) (A and B), which co-circulate with alternating predominance (Baek; Komoyo; Reiche and Schweiger; Venter). RSV is the principal pathogen responsible for LRTI in infants and young children, estimated to cause up to 90% of childhood bronchiolitis and up to 40% of paediatric pneumonias (Hall 2001). In infants <1 yr of age, mean hospitalisation rates for RSV infection in the US were 16 times higher than rates for influenza (Zhou). Among children 0 to 3 yrs of age, RSV hospitalisation rates were found to be 4 and 9 times greater than the hospitalisation rates associated with parainfluenza and influenza,

respectively (Forster). Furthermore, the excess respiratory mortality rate among infants in the US was 5-fold higher for RSV vs. influenza (Hansen). RSV LRTI is a serious and potentially life-threatening disease characterised by infection and inflammation of the alveoli and bronchioles. It is associated with necrosis and sloughing of the epithelium of the small airways, with oedema and increased secretion of mucous. This can lead to airway obstruction and a typical clinical picture of hyperinflation, atelectasis, and wheezing (Hall 2001). It is most severe when the disease occurs in the first year of life associated with smaller airway diameter in infants. Known factors increasing the risk of hospitalisation with RSV include male sex, age under 6 mths, crowding, siblings and day-care exposure (Bont). All infants, including healthy infants born at term, are at risk for severe RSV LRTI with primary RSV infection in infancy. RSV LRTI is the most common reason for admission to hospital in infants <1 yr of age (Hall 2001; Hall 2012; Murray; Rha). In Australia, 73% of hospitalisation due to RSV are aged <1 yr (Ranmuthgala). Otherwise, healthy infants accounted for ≈80% of RSV hospitalizations in this age gp (Homaira). The majority of infants admitted to hospital with RSV LRTI are born at term and have no underlying serious comorbidity, as illustrated with data from Europe and North America (Hall 2012; Murray; Bont; Rha). Some infants with serious underlying comorbidities remain vulnerable for severe RSV disease beyond their first RSV season, these include infants with prematurity, CLD, CHD, cystic fibrosis, neuromuscular conditions, Down syndrome, or immunocompromised states (including congenital or acquired, e.g. through anticancer chemotherapy or organ transplantation) (Chaw 2020a; Chaw 2020b; Resch; Manzoni). Lung immaturity, impaired vascular or pulmonary function, inability to clear secretions, or immunocompromised states can all exacerbate the pathophysiology of RSV LRTI increasing the severity of the disease (Chaw 2020a; Chaw 2020b). Immunocompromised children may experience particularly severe disease, with prolonged hospitalisation and high Intensive Care Unit (ICU) admission rates (Asner; Moyes; Manzoni). Furthermore, RSV associated mortality rates can reach 60% in untreated children with immunodeficiencies, compared to <0.5% in healthy infants with RSV (Asner; Moyes). The burden of paediatric RSV disease is focussed on the first yr of life. Average annual RSV-coded admission rates ranged from 8.6 to 22.3 per 1000 children aged <1 yr across 7 EU countries, whereas rates ranged from 0.2 to 2.24 per 1000 in children aged 1 to 4 yrs. Admissions peak in the second mth of life but are considerable throughout infancy (Reeves). Comparable rates and patterns were derived from a systematic review of epidemiological studies in North America and Europe (Bont). Annual hospitalisation rates for RSV-associated acute respiratory infections in the first year of life ranged from 3.2/1000/yr to 42.7/1000/yr and decreased with increasing age to 0.6/1000/yr to 1.78/1000/yr in children aged 1 to 4 yrs. In Australia the annual hospitalisation rate has been estimated as from 8.7 to 17.4 per 1000 infants in the first yr of life (Ranmuthgala). Reported rates of RSV associated hospitalisation vary considerably between studies and across seasons within the same study (Bont).

Outpatient burden also extends throughout the first year of life (Lively; Forster). Disease managed in the outpatient setting is almost as severe as that in the hospital setting, with laboured respiration in 73% and 85% of children with office or emergency room (ER) visits, respectively (Hall 2009). In a study in the US, RSV accounted for 18% of ER visits and 15% of outpatient visits for acute respiratory infections in children <5 yrs of age during the RSV season (Hall 2009). In England, among children <5 yrs of age, 16% of all General Practitioner consultations for acute respiratory illness throughout the year were attributed to RSV (Cromer). There is a considerable community burden imposed by RSV in infancy in Australia. One community-based cohort study on healthy children found that 94% of healthy children showed immunological evidence of RSV infection by the age of 3, 73% of infections were symptomatic, 56% of those attended primary care as result, and 3% required hospitalisation (Takashima). Comparison with the health burdens attributed to the influenza virus and rotavirus suggests that the disease burden caused by RSV is potentially much higher (Saravanous).

Seasonality RSV occurs in largely predictable annual epidemics. Globally, RSV activity showed a latitudinal gradient in the timing of epidemics in each hemisphere (Li 2019). In temperate

climates, RSV infections have occurred primarily during the autumn, winter and spring, with a typical duration of 5 months (a typical season). In temperate regions of Australia where the majority of the pop'n resides, RSV circulation typically begins in March/April and peaks in July/August each yr (NSW Health 2020). In subtropical regions RSV circulates yr round but increases in correlation with periods of high rainfall and humidity (Fagan). RSV activity dramatically declined globally during the 2020/2021 Northern Hemisphere (NH) and 2021 Southern Hemisphere (SH) seasons, as COVID-19 mitigation measures impacted RSV circulation. As exposure decreased, there was an increase in the susceptible pop'n of infants and children who did not have the typical level of exposure during COVID-19 restrictions. Epidemiological models predicted that this increase in RSV susceptibility would affect the timing and increase the severity of future RSV incidence (Baker). Such off-season outbreaks occurred widely (CDC 2021a; CDC 2021b; van Summeren; Williams). Potential drivers of RSV rebound and out-ofseason epidemics included re opening of schools and increased pop'n susceptibility (Li 2022b). In Australia, "out of season" outbreaks of RSV have been observed more frequently in recent yrs and the magnitude of outbreaks has been higher due to the interruption of disease exposure in young infants and toddlers due to the effect of extended lockdowns and social distancing utilised to manage COVID-19 (Eden).

2.2. Current treatment options

In regard to the current RSV therapies in Australia:
1) Ribavirin is registered in Australia, however it is not registered for use in RSV;
2) For prevention - Synagis (palivizumab) a humanised RSV mAb directed against the F protein of RSV (Johnson) is approved. With a half-life of ≈one mth, the 50mg & 100mg solution for injection vials are registered with the following TGA approved (1999) indication and dosing recommendations. **Indications**: For the prevention of serious LRTI caused by RSV in children at high-risk of RSV disease. Safety and efficacy were established in children with bronchopulmonary dysplasia (BPD), infants with a history of prematurity (gestational age less than or equal to 35 weeks at birth) and children with haemodynamically significant congenital heart disease. **Dose and administration:** 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season and subsequent doses should be administered monthly throughout the RSV season. To avoid risk of reinfection, it is recommended that children receiving palivizumab who become infected with RSV continue to receive monthly doses of palivizumab IM for the duration of the RSV season. The burden of mthly healthcare visits during the season can be a barrier to compliance (Wong). Moreover, palivizumab is not funded in Australia under the Pharmaceutical Benefits Scheme (PBS). It is funded by the Western Australian Department of Health for infants and young children in the categories outlined above. In other jurisdictions access is discretionary on a case-by-case basis.

2.3. Clinical rationale

Prevention (Giersing) of severe RSV RTI is the main approach as there is still no registered vaccine (Ruckwardt) despite decades of effort and management of RSV infection as both an outpatient and inpatient is essentially supportive (Baraldi; Turnham) as there are no approved treatments. Bronchodilators and corticosteroids have not shown a benefit for RSV bronchiolitis (NICE 2021; Corneli; Kerr; Fernandes; Gadomski and Scribani; Fogelman). The only currently approved prophylaxis for RSV is palivizumab (SYNAGIS), registered only for infants at the highest risk for severe RSV disease (See above for indication).

2.4. Formulation

2.4.1. Formulation development

RSV is a member of the *Pneumoviridae* family (Rima), and is a non-segmented, negative-sense, enveloped RNA virus, classified into two subtypes, A and B, based on sequence homology of the RSV surface glycoprotein G (Wertz and Moudy). Viral entry into host cells and cell-to-cell spread is dependent on the fusion (F) protein, which mediates fusion of the viral and host cell membranes (Walsh 1984; Walsh 1989; Hall and McCarthy 1995). The F protein is a highly conserved protein across RSV subtypes (Wertz and Moudy) and is synthesised as an inactive precursor (F0) that is cleaved by host cell proteases into the biologically active, disulfide-linked F1 and F2 subunits. The F protein is expressed on virions in a pre-fusion conformation. Juxtapositioning of the virus and host cell membranes leads to the F protein-mediated fusion event and the accompanying irreversible refolding of F protein into a post-fusion conformation (Chang and Dutch). Six antigenic sites (Ø and I–V) have been identified in prefusion and/or postfusion F proteins (Gilman) with target epitopes for prophylactic neutralising mAbs (Broadbent). The majority of the neutralising activity detected in a human IgG preparation (i.e. RespiGam) is directed against the pre-fusion conformation of RSV F (Magro). The F protein is a clinically validated target for immunoprophylaxis of RSV disease. Nirsevimab (MEDI8897), a recombinant neutralising human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology, was derived from a human monoclonal antibody D25 (Kwakkenbos) that was isolated directly from human B cells and binds the prefusion conformation of the RSV F protein (McLellan). D25 was affinity optimized for RSV neutralisation potency in vitro to generate 1G7. Nirsevimab differs from 1G7 by a three amino acid substitution, M257Y/S259T/T261E (M252Y/S254T/T256E, according to the EU numbering system), referred to as "YTE", in the heavy chain CH2 fragment crystallizable (Fc) region of the mAb. The YTE modification was added to the mAb to prolong the terminal half-life of the antibody in humans (Griffin 2017; Robbie). 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-cell fusion. The cell culture neutralisation activity of nirsevimab against RSV was measured in a dose-response model using cultured Hep-2 cells. Nirsevimab neutralised RSV A and RSV B isolates with median EC_{50} values of 3.2 ng/mL (range 0.48 to 15 ng/mL) and 2.9 ng/mL (range 0.3 to 59.7 ng/mL), respectively. The clinical RSV isolates (70 RSV A and 49 RSV B) were collected between 2003 and 2017 from subjects across the US, Australia, Netherlands, Italy, China and Israel and encoded the most common RSV F sequence polymorphisms found among circulating strains. Nirsevimab demonstrated *in vitro* binding to immobilised human FcγRs (FcγRI, FcγRIIA, FcγRIIB, and FcγRIII) and equivalent neutralising activity compared to parental monoclonal antibodies, IG7 and IG7-TM (Fc region modified to reduce FcR binding and effector function).

Summary of Biopharmaceutic Studies and Associated Analytical Methods

These are summarised in **Module 2.7.1** Summary of Biopharmaceutic Studies and Associated Analytical Methods AstraZeneca Nirsevimab. Bioanalytical methods for quantitation of drug concentration (conc'n), Anti-drug antibody (ADA) against nirsevimab, ADA against palivizumab, nAb to nirsevimab, ADA to YTE, RSV-neutralising antibody, RSV seroresponses, RSV detection, RSV subtyping, and RSV genotypic and phenotypic resistance characterisation were developed and validated and are summarised in **Module 2.7.1** of the Application.

Pre-clinical (see Module 2.4. Nonclinical Overview for the summary): 16 nonclinical studies were performed to characterise mechanism of action, antiviral activity (in vitro and in vivo), antiviral resistance (in vitro), pharmacokinetics (PK) and safety of nirsevimab: 11 nonclinical pharmacologic studies; a nonclinical PK study; 3 GLP nonclinical toxicologic studies (1 toxicity study and 2 tissue cross-reactivity studies). Overall, no nirsevimab-related safety concerns were revealed in the pre-clinical setting.

The manufacturing process will be reviewed in detail by the **Module 3** reviewer. The manufacturing process is also summarised in **Modules 2, see Module 2.3.P Quality Overall Summary for Drug Product Nirsevimab and 2.3.S Quality Overall Summary for Drug Substance Nirsevimab**.

Table 1. Composition of Drug Product (50 mg/pre-filled syringe)

Ingredient	Unit Formula *	Purpose	Quality Standard	Concentration
Active Ingredient				
Nirsevimab	50 mg	Active	In-house Reference Standard	100 mg/mL
Excipients				
L-Histidine	1.1 mg	Formulation buffer	USP-NF, Ph. Eur., JP	14.3 mM
L-Histidine hydrochloride monohydrate	1.6 mg	Formulation buffer	Ph. Eur., JP	15.7 mM
L-Arginine hydrochloride	8 mg	Stabilizer	USP-NF, Ph. Eur., JP	80 mM
Sucrose	21 mg	Cryoprotectant	USP-NF, Ph. Eur., JP	120 mM
Polysorbate 80	0.1 mg	Surfactant/stabilizer	USP-NF, Ph. Eur., JP	0.02% (w/v)
Water for Injection (WFI)	Approximately 440 mg	Aqueous vehicle	USP-NF, Ph. Eur., JP	Approximately 49 M

JP = Japanese Pharmacopeia; NF = National (United States) Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

* Unit formula is based on the label-claim volume of 0.5 mL.

Table 2. Composition of Drug Product (100 mg/pre-filled syringe)

Ingredient	Unit Formula *	Purpose	Quality Standard	Concentration
Active Ingredient				
Nirsevimab	100 mg	Active	In-house Reference Standard	100 mg/mL
Excipients				
L-Histidine	2.2 mg	Formulation buffer	USP-NF, Ph. Eur., JP	14.3 mM
L-Histidine hydrochloride monohydrate	3.3 mg	Formulation buffer	Ph. Eur., JP	15.7 mM
L-Arginine hydrochloride	17 mg	Viscosity modifier	USP-NF, Ph. Eur., JP	80 mM
Sucrose	41 mg	Cryoprotectant	USP-NF, Ph. Eur., JP	120 mM
Polysorbate 80	0.2 mg	Surfactant/stabilizer	USP-NF, Ph. Eur., JP	0.02% (w/v)
Water for Injection (WFI)	Approximately 880 mg	Aqueous vehicle	USP-NF, Ph. Eur., JP	Approximately 49 M

JP = Japanese Pharmacopeia; NF = National (United States) Formulary; Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

* Unit formula is based on the label-claim volume of 1.0 mL.

2.4.2. Excipients

L-histidine; L-histidine hydrochloride; L-arginine hydrochloride; Sucrose; Polysorbate 80; Water for injections. For exact quantities per pre-filled syringes see **Table 1 and 2**.

2.5. Regulatory history

2.5.1. Australian regulatory history

This is a new drug application.

2.5.2. Orphan drug designation

This is not an orphan drug.

2.5.3. Related submissions

Not applicable.

2.5.4. Overseas regulatory history

Table 3 provides a list of major countries in which a similar application has been submitted and/or approved. A similar application has not yet been submitted in Canada, Switzerland, New

Zealand or Singapore. There have been no deferrals, withdrawals or rejections in major countries in which a similar application has been submitted, including Canada and the US Although the Applicant did not provide an updated approval status in the 'erratum' documents submitted to the TGA in Dec 2022, as detailed above, Nirsevimab has now been approved in the EU for the same indication as is being sought in Australia. In addition, it has been approved in GB, with a date of first authorisation: 07-Nov-2022. The Table below provided by the Applicant was not updated to reflect the recent EU and GB authorisations.

Table 3. Submission and approval status: Nirsevimab

Country	Submission date	Approval date	Comment
Canada	Planned Q4/22		
European Union [a]	28 JAN 22	*CHMP Opinion 15SEP22 EC decision expected 10 NOV22*	Accelerated assessment and PRIME The EU submission was based on an earlier subset of some of the primary studies (ie first season dossier). Draft SmPC (as agreed at CHMP positive opinion) provided[c] in Module 1.11.2.
	Planned 1Q/22		Type II variation – second season dossier
Switzerland	Planned Q4/22		
Great Britain [b]	20 SEP 22		First season dossier submitted to MHRA via the *European Commission Decision reliance Procedure*.
	Planned 1Q/22		Type II variation – second season dossier
United States	26 SEP 22	-	Priority review requested as part of the BLA submission.

[a] Centralised Procedure Rapporteur (Denmark) and co-rapporteur (Germany).
[b] National application via reliance pathway
[c] As provided to TGA as part of the COR-B briefing document submitted 19 SEP 22

2.6. Guidance

In the original submission, AstraZeneca provided the assurance that the Application is consistent with the pre-planning pre-submission form (PPF) in scope and scale, with the following exceptions:

- ***Module 1****:* The PI has been updated to now include the Section 5.1 information. Other amendments have also been made (see **Module 1.3.1.2** for further information).
- ***Module 3****:* Two documents have been removed in the submission:
  - S.2.6.3.5: included in error in the PPF TOC (EU specific requirement not intended for the international/US dossier)
  - P.7 Notified body opinion: duplicate copy removed as already included in the 3.2.R (provided for information only for Australia, prefilled syringe not regulated as a device).

Additionally, on 13-Dec-2022 further information and updated documents were submitted to the TGA, as follows: Updates to **Module 1.11.1** Foreign regulatory status updated to include EU and GB approvals, as well as other relevant submissions made in Q4/22; updates to 1.11.2 Approved EU QRD Replaces the close-to-approved draft provided in sequence 0000; approved GB Summary of Product Characteristic (SmPC) New document. The Applicant decided not to submit the approved EU-Risk Management Plan (RMP) with these updated documents. The only difference between the version submitted to the TGA (v1s4) and that approved by the EMA (v1s5) was the addition of the Qualified Person responsible for PharmacoVigilance (QPPV) information. Hence, no update to the Australian-Specific Annex (ASA) was submitted at this point, instead the Applicant proposed to update the ASA as part of the MS3 S31 response package to the RMP evaluation.

Other updated documents submitted at this time were as follows:

Nonclinical and Clinical errata/addenda

- previously notified Clinical errata for Module **2.7.3** and **5.3.5.1** Study **D5290C000005** (**MEDLEY)** i.e.
1) Erratum for Module **2.7.3** Summary of Clinical Efficacy corrects one data error in Section 3.4, Table 36;
2) REVISED VERSION - includes correction from erratum;
3) Post submission it was noted that certain IEMT tables referred to within the interim Clinical Study Report (iCSR) for **MEDLEY** were inadvertently omitted. These have now been included as part of the accompanying **MEDLEY** iCSR errata. This erratum for the **MEDLEY** iCSR – Season 2 Analysis corrects Appendix 16.2.10 to include IEMT 89 and IEMT 97 (referenced in **CSR Section 12.1.2.2.5**) and IEMT 123 (referenced in **CSR Section 12.3.2.1**), which were inadvertently omitted in the original version.
Note to evaluators – Nonclinical and Clinical errata, as requested by the Case Manager.
- In addition, the following errata/amendments have also been included in Nonclinical and Clinical errata: **Module 2.6.2** Pharmacology Written Summary errata and **Module 5.3.5.4** Virology Study Report **ID8897O-1617** amendment i.e.
1) Post submission a data error was identified in 2.6.2 Pharmacology Written Summary. The correction included in this erratum relates to a report reference supporting the collected samples in China for determining antiviral activity of nirsevimab/1G7 against RSV A and B clinical isolates in Section 2.3.1.2 of the document. The corrections listed are not felt to impact overall conclusions on efficacy and safety;
2) Virology Study Report **ID8897O-1617**: Genotypic and Phenotypic Analysis of RSV Strains Collected from the OUTSMART-RSV Surveillance study During the 2016-2017 (YEAR 2) RSV Season. Post submission it was noted that there was an error in IC_{50} values for clinical strains Osmt17-0433 F2 P101L, Osmt17-0210-B046, and Osmt17 0989-B047 within Report ID8897O-1617 which is provided in Module **5.3.5.4**. An amendment to Report ID8897O-1617 (amendment 2) has been provided in Module **5.3.5.4** of this sequence, which now details the corrected values for these isolates.

Table 4. LIFECYCLE MANAGEMENT TRACKING TABLE

Sequence	Sequence type	Sequence description	Related sequence	Date
0000	A- NBE New Biological Entity	Initial	0000	OCT 2022
0001	Supplementary information	Response to request for information *[MS2 RFI (30NOV22) response + M5 errata & UK/GB approval documentation]*	0000	DEC 2022

2.7. Evaluator's commentary on the background information

This was comprehensive and informative regarding the epidemiology and clinical problems presented by RSV in children in Australia and globally. This background information highlights the global unmet needs for both treatment and prevention of RSV.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical data package for this submission includes 3, pivotal, double-blind, randomised studies (**Study 3** [**D5290C00003**], **MELODY** [**D5290C00004]** and **MEDLEY** [**D5290C00005**]) and an open-label study in immunocompromised infants/children (**MUSIC** [**D5290C00008**]). The clinical data package also includes 2 completed dose-escalation, safety, PK and ADA studies (**Study 1** [**D5290C00001**] and **Study 2** [**D5290C00002**]), which (along with **MELODY, Study 3,** and **MEDLEY**) contributed data for population PK (popPK) modelling. Australian sites participated in **Study 3** and **MELODY**. Integrated summaries of efficacy, safety and immunogenicity have been included in support of the clinical data. In summary, the Application includes:

Module 1: Administrative documents, draft PI & Consumer Medicine Information (CMI) for Australia; EU SmPC, GB PI, EU-RMP Vn., Number 1 Succession 4, Data lock point 03-May-2021 and the ASA Vn. Number 1.
Module 2: Integrated Summaries (biopharm, clinical efficacy, clinical pharmacology, safety). Non-clinical overview and summaries; literature references; synopses-individual-studies.
Modules 3 and 4: Provided for information for the clinical reviewer.
Module 5: 6 studies in support of the Category 1 Application as detailed in **Table 5**.

Table 5. Studies Contributing to the Nirsevimab Clinical Package

Study number (abbreviation) Status	Study design (primary/secondary objectives)	Study population	Dosing regimen	Number randomised (dosed) by analysis
Completed				
D5290C00001 (Study 1)	Phase I, dose escalation, randomised, double-blind, placebo-controlled- (safety, PK, and ADA)	Healthy adults, aged ≥ 18 to < 50 years.	**Nirsevimab:** 300, 1000, or 3000 mg single IV dose 100 or 300 mg single IM dose **Placebo:** single IM/IV dose	**Nirsevimab:** 102 (102) Reordered this footnote to follow lettered footnotes. 34 (34)
D5290C00002 (Study 2)	Phase Ib/IIa, dose escalation, randomised, double-blind, placebo-controlled- (safety, PK, and ADA)	Preterm infants born 32 to < 35 wGA entering their first RSV season	**Nirsevimab:** 10, 25, or 50 mg single IM dose **Placebo:** single IM dose	**Nirsevimab:** 71 (71) **Placebo:** 18 (18)
D5290C00003 (Study 3) Pivotal	Phase IIb, randomised, double-blind, placebo-controlled, (efficacy, safety, PK, and ADA). Primary efficacy endpoint = MA RSV LRTI; secondary endpoint = MA RSV LRTI with hospitalisation.	Very and moderately preterm infants born ≥ 29 to < 35 wGA, entering their first RSV season 23 countries, including US.	**Nirsevimab:** 50 mg single IM dose **Placebo:** single IM dose	**Final Analysis** [a] **Nirsevimab:** 969 (968) (including 570 [572][b] infants weighing < 5 kg randomised to the proposed dose) **Placebo:** 484 (479) (including 290 [288] infants weighing < 5 kg randomised to the proposed dose)
Study number (abbreviation) Status	**Study design (primary/secondary objectives)**	**Study population**	**Dosing regimen**	**Number randomised (dosed) by analysis**
Ongoing				
D5290C00004 (MELODY) Pivotal • **Primary Cohort** (complete; all subjects followed up to Day 511). • **Safety Cohort** (all subjects followed up to at least Day 151; follow-up ongoing to Day 511).	Phase III, randomised, double-blind, placebo-controlled (efficacy, safety, PK, and ADA). Primary efficacy endpoint = MA RSV LRTI; secondary endpoint = MA RSV LRTI with hospitalisation.	Term and late preterm infants born ≥ 35 wGA, entering their first RSV season. 21 countries, including US and Japan.	**Nirsevimab:** 50 mg (infants < 5 kg) or 100 mg (infants ≥ 5 kg) single IM dose. **Placebo:** single IM dose.	**Primary Analysis** [b] **Primary cohort:** • **Nirsevimab:** 994 (987) • **Placebo:** 496 (491) **Safety Analysis** [c] **Primary cohort:** • As above **Safety cohort:** • **Nirsevimab:** 1015 (1011) • **Placebo:** 507 (505) **All subjects:** • **Nirsevimab:** 2009 (1998) • **Placebo:** 1003 (996)
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).	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)** [d] **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** [e] **CLD/CHD cohort:** • Nirsevimab/nirsevimab [f]: 180 (180) • Palivizumab/nirsevimab [f]: 40 (40) • Palivizumab/palivizumab [f]: 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)	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:** 200mg single IM dose	**Interim analysis:** [g] A total of 60 non-randomised, immunocompromised subjects who received the proposed dose of nirsevimab (35 subjects in the first year of life and 25 subjects in the second year of life) [i].

Footnote: [a]Study 3 Final Analysis was conducted on data from all randomised subjects through 360 days post dose, when all subjects had completed the final study visit. Two subjects randomised to placebo incorrectly received nirsevimab; both were included in the as-treated population under the nirsevimab gp; [b] **MELODY** Primary Analysis (DCO 11-Mar-2021) was triggered when all randomised subjects in the Primary Cohort had been followed up through at least 360 days post dose. The Primary Analysis included data through 150 days post dose for efficacy and constituted the final analysis for efficacy in the Primary Cohort; [c]**MELODY** Safety Analysis (DCO 31-Mar-2022) was triggered when all randomised subjects in the Safety Cohort had been followed up through at least 150 days post dose. The Safety Analysis included data through 150 days post dose for efficacy and through at least 150 days post dose for safety, PK, ADA, RSV nAbs, and RSV serology in the Safety Cohort. This was the final analysis for efficacy and constituted the final analysis for efficacy in the Safety Cohort, as reported in the **MELODY** iCSR. In addition, the Safety Analysis included safety, PK, ADA, RSV nAbs, and RSV serology data collected through 510 days post dose in the Primary Cohort. All available safety, PK, ADA, RSV nAbs, and RSV serology data were pooled for the Primary and Safety cohorts, as reported in the **MELODY** iCSR; [d]**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, as reported in the **MEDLEY** iCSR; [e] 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; [f] 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); [g] **MUSIC** Interim Analysis (DCO 16-May-2022) was triggered when all subjects, enrolled globally by end of 2021, were followed through 150 days post dose. All safety, PK, ADA, and descriptive efficacy data collected for these subjects were included in the Interim Analysis, as reported in the **MUSIC** iCSR; [h] Two subjects randomised to placebo received nirsevimab in error; [i] One subject aged ≥ 12 mths received the 50 mg/100 mg dose but was included in the 'second year of life' total.

3.2. Paediatric data

This Application is comprised of mostly paediatric data. However, **Study 1** was a PK study conducted in healthy adults aged ≥18 yrs to <50 yrs.

3.3. Good clinical practice (GCP)

Sponsor procedures, internal quality control measures, and audit programmes provide reassurance that the clinical programme was carried out in accordance with GCP, as recommended by the International Council for Harmonisation.

3.4. Evaluator's commentary on the clinical dossier

This was appropriate for a Category 1 Application.

4. Pharmacokinetics

MEDI8897 has no endogenous targets and thus, no dose-limiting toxicities are expected at any dose level. The 2 completed dose-escalation, safety, PK and ADA studies **Study 1** and **-2**, are described in **Section 19.1.1** of this report. PK data from these first two studies, along with **Study 3, MELODY** and **MEDLEY** contributed data for popPK modelling (**Section 19.1.2.1** of this report). The doses of MEDI8897 in **Study 1** (first-in-human) were based on results of a Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys, preclinical efficacy data from cotton rat pharmacology studies, a popPK model developed for palivizumab (Robbie), and US Food and Drug Administration (FDA) guidelines.

4.1. Studies providing pharmacokinetic information

Table 6. Submitted PK studies.

PK topic	Subtopic	Study ID	*	Synopsis
Healthy adults	General PK - Single dose	**D5290C00001**	*	Section **19.1.1.** of this report
Special pop'ns	Target pop'n §- Single dose	**D5290C00002**	*	
PopPK analyses	Target pop'n including immuncompromised children in **MUSIC**	**D5290C00001; D5290C00002; D5290C00003; D5290C00004; D5290C00005; D5290C00008**		Section **19.1.2.1.** of this report

* Indicates the primary PK aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Nirsevimab is a human mAb i.e. a protein and has to be administered systemically by injection. Its PK characteristics have been determined based on data from the nirsevimab clinical studies detailed in **Table 5**.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanism of absorption

Following IM administration, the median (range) time to maximum conc'n was 6 (1 to 28) days. The estimated absorption $t_{1/2}$ was 1.7 days, and the estimated absolute bioavailability was 84%.

4.2.2.2. Bioavailability

The PK of nirsevimab were dose-proportional following single IV doses of 300 to 3000 mg and single IM doses of 100 mg to 300 mg in adults. In infants, dose-proportional PK was seen after single IM doses of 25 mg to 50 mg (see also **Section 19, Studies -1 and -2**).

4.2.2.3. Distribution

Volume of distribution – derived from PopPK

The estimated central and peripheral volumes of distribution (V_{diss}) of nirsevimab were 216 mL and 261 mL, respectively, for a typical 5 kg infant aged 11.1 mths.

4.2.2.4. Metabolism

Interconversion between enantiomers

Not Applicable.

Sites of metabolism and mechanisms / enzyme systems involved

Nirsevimab, as a human mAb is degraded by proteolytic enzymes widely distributed in the body. Nirsevimab is not metabolised by hepatic enzymes.

Non-renal clearance

No clinical studies were conducted to investigate the effect of renal or hepatic impairment on nirsevimab. Monoclonal antibodies are not primarily cleared via the renal or hepatic pathway and change in these functions are therefore not expected to influence nirsevimab clearance.

Metabolites identified in humans: active and other PK of metabolites and Consequences of genetic polymorphism

Not applicable.

4.2.2.5. Excretion

Routes and mechanisms of excretion

As a typical mAb, nirsevimab is eliminated by intracellular catabolism with no evidence of target-mediated systemic clearance (CL) (note: the target of nirsevimab is exogenous). The estimated CL for nirsevimab was 3.42 mL/day for a typical 5 kg infant with a postmenstrual age of 11.1 mths. The predicted mean (SD) terminal elimination half-life in infants was 71.4 (11.4) days.

Mass balance studies

Not performed.

Renal clearance

Monoclonal antibodies are not primarily cleared via the renal or hepatic pathway and change in these functions are therefore not expected to influence clearance of this mAb.

4.2.2.6. Intra and inter individual variability of pharmacokinetics

Based on popPK analysis, nirsevimab clearance is dependent on body weight and post-menstrual age. There were no clinically relevant effects of race, ADA, or concomitant CLD or CHD on PK. Gender was not evaluated for influence on nirsevimab PK as differences in children ≤2 yrs of age are not expected. See **Section 3.4, Module 2.7.2** of the Application for more detail. Nirsevimab serum conc'ns in immunocompromised children entering their first or second RSV season (**MUSIC**) were similar to non-immunocompromised infants and children (see **Section 19.1.2.1** of this report).

4.2.3. Pharmacokinetics in the target population

PK of nirsevimab in healthy preterm infants born ≥32 to <35 wGA was evaluated in **Study 2** (**Section 19.1.1** of this report). Exposure increased in a less than dose-proportional manner from 10 mg to 25 mg (assessment likely influenced by the difference in sample sizes for these dose gps), and approximately dose-proportionally from 25 mg to 50 mg. The mean terminal t½ in serum ranged from 62.5 to 72.9 days across IM doses (**see also Section 11.4.4.1, Study 2 CSR, Module 5.3.3.1 for further information**).

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

Not assessed.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

Not assessed.

4.2.4.3. Pharmacokinetics according to age

Nirsevimab has been studied in adults and preterm and term infants. An effect of postmenstrual age was estimated in the popPK analysis. There is a high correlation between age and body weight in children.

4.2.4.4. Pharmacokinetics related to genetic factors

Not assessed.

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

Not assessed.

4.2.5. Population pharmacokinetics

4.2.5.1. PopPK analysis ID

See **Section 19.1.2.1** of this report**.** Overall, the parameter estimates were similar across the dataset updates. A 2-compartment linear disposition model with first order absorption and elimination adequately described the PK of nirsevimab after IV and IM administration across the age, body weight, and dose range studied. Body weight was the main covariate influencing PK, implemented using estimated allometric exponents. In addition to body weight, a maturation effect on CL (implemented using postmenstrual age) was included to account for the differences in PK in infants versus (vs.) adults. To adequately predict the PK in children in RSV Season 2, a categorical covariate was included estimating a relatively lower CL than expected based on body weight and postmenstrual age in Season 2. Further, race and ADA status were identified as statistically significant covariates. Parameter estimates of the final nirsevimab popPK model across infants and adults are presented in **Table 7.**

The elimination and distribution clearances (CL and Q) and central and peripheral volumes of distribution were 3.42 mL/day, 150 mL/day, 216 mL, and 261 mL, respectively, for a typical infant who is 5 kg, White, ADA negative, and a postmenstrual age of 11.1 mths at the time of dose administration in RSV Season 1. Bioavailability (F) and absorption rate constant (KA) after IM administration were 84% and 0.401 day -1, respectively, corresponding to an absorption t½ of 1.7 days (note: these are defined primarily based on adult data but are assumed to be the same in infants). Interindividual variability implemented on CL, central volume, and KA, were 26%, 43%, and 44%, respectively. The parameters were estimated with adequate precision (relative standard error ≤30%) (see also **Section 4.2.2.4, 2022 population PK report**, **Module 5.3.3.5**) and **Section 19.1.2.1** of this report**.**

Table 7. Summary of Final Population PK Model Parameter Estimates

Parameters	Estimates	%RSE	Bootstrap 95% CI
Clearance (CL, mL/day) [a]	38.8	6	29.9, 43.9
Central volume (Vc, mL) [a]	1980	10	567, 2760
Intercompartmental clearance (Q, mL/day) [a]	709	9	462, 872
Peripheral volume (Vp, 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, 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 (Vc, Vp) [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, American Indian or Alaskan Native, Multiple races) [e]	CL_{pop}* (1 - 0.0894)	30	-0.123, -0.0545
Race effect on volume of distribution (Asian, American Indian or Alaskan Native, Multiple races) [e]	Vc_{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
ηVc-ηCL correlation	r = 0.785	-	-
IIV on Vc	43	4 [29%]	32, 90
IIV on KA	44	8 [83%]	16, 78
Residual Error	**Estimates**	**%RSE**	**Bootstrap 95 % CI**
Proportional error	21%	1	20, 22

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

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

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

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; $t_{1/2}$ = half-life; Vc_{pop} = typical central volume; Vc = central volume; Vp = peripheral volume, WT = body weight.

Source: Table 9, 2022 population PK report, Module 5.3.3.5.

4.2.6. Pharmacokinetic interactions

Nirsevimab is an RSV specific mAb and as it does not have a host target is not expected to have drug-drug interactions or interfere with immune responses to co-administered vaccines. See also **Section 8.5.2** of this report.

4.2.7. Clinical implications of *in vitro* findings

The exposure response of nirsevimab, evaluated based on **Study 3 and MELODY**, demonstrated a positive correlation between AUC (derived from CL at baseline) and a reduction in the risk of MA RSV LRTI through 150 days post dose with a target AUC of 12.8 mg*day/mL. Weight-band

dosing (50 mg for infants weighing <5 kg and 100 mg for infants weighing ≥5 kg at the time of dosing) resulted in exposures above the target in >95% of the infants studied in **MELODY**. No further relationship between nirsevimab exposure and the risk of medically attended (MA) LRTI was evident based on data from the weight-band dose, supporting the adequacy of the selected dose regimen. Exposure-safety analysis was not conducted, as there was no identified safety signal in the nirsevimab programme or evident safety concerns associated with the highest nirsevimab exposures i.e. infants weighing <2.5 kg on Day 1 who received the proposed nirsevimab weight-band dose (50 or 100 mg) in RSV Season 1 or infants who received 200 mg in RSV Season 2, including those weighing <7 kg.

4.3. Evaluator's overall conclusions on pharmacokinetics

The Applicant has established the PK parameters of single dose nirsevimab in healthy adults and healthy pre-term infants in **Studies -1 and 2** (see also **Section 19** of this report). The design of these studies with a one-year follow-up allowed the durability of the anti-RSV neutralising Ab (nAb) to be defined. The confirmed long half-life lends itself to a single dose providing adequate cover for the length of an average RSV season (i.e. 5 mths). Subsequently, a popPK model was developed based on data pooled from Studies **-1, -2, -3, and MELODY (Primary Cohort).** Individual exposure parameters were derived and used to evaluate exposure response for the primary efficacy endpoint (MA RSV LRTI) through 150 days post dose in the pivotal efficacy studies (**Study 3, and** MELODY [Primary Cohort]), and define an efficacious exposure target. This model was sequentially updated with data from **MEDLEY (RSV Season 1 and 2**) to support PK extrapolation of efficacy to the **MEDLEY** pop'n. Individual exposures in the **MEDLEY**, including preterm infants (RSV Season 1) and infants and children with CLD/CHD (RSV Seasons 1 and 2), were derived and compared with the exposure target. PK were also evaluated in immunocompromised infants and children entering RSV Season 1 or 2 in **MUSIC**, to support PK extrapolation to these highly vulnerable popn's (See also **Section 19.1.2.1**. of this report). As expected, for this class of drugs, body weight is an important covariate on the PK of nirsevimab. Clearance and volume of distribution increase with increasing body weight. To evaluate the impact of body weight across the expected body weight range in the relevant infant pop'n, simulations were performed to predict nirsevimab exposures for a 50 mg dose down to 1 kg at the time of dosing, and a 200 mg dose (in Season 2) down to 6.5 kg. Compared with an infant weighing 5 kg and receiving a 100 mg dose, the smallest infants (1 kg) receiving 50 mg are predicted to have ~84% higher C_{max}, ~25% higher $AUC_{0\text{-}365}$, and ~9% lower conc'ns at Day 151. Importantly, predicted exposures (C_{max} and $AUC_{0\text{-}365}$) in a 1 kg infant are considerably lower (≈3-fold) than those achieved in adults following an IV dose of 3000 mg. These results suggest that the 50 mg dose is expected to be safe and efficacious across the body weight range ≥1 kg. Predicted exposures following 200 mg dose in Season 2 are also within the range of safe and efficacious exposures.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

5.1.1. Mechanism of action

Nirsevimab is a humanised monoclonal antibody (i.e. a passive immunotherapy) which neutralises RSV by binding the prefusion conformation of the RSV F protein at a discontinuous site (AA 62–69 and 196–212) within antigenic site Ø (AA 62–96 and 195–227), thus preventing the RSV F protein from mediating fusion between the viral and cellular membranes. Sequence analysis revealed that most of the amino acids in the nirsevimab binding site have been well conserved (>99%) at 24 of the 25 positions in RSV A and at 22 of the 25 positions in RSV B. Since 2015, most amino acid residues in the nirsevimab binding site have remained highly conserved (>99%) at all 25 positions in RSV A and 22 of the 25 positions in RSV B (**see Report ID8897-0102, Module 5.3.5.4**).

5.1.2. Pharmacodynamic effects

5.1.2.1. Primary pharmacodynamic effects

This mAb mode of action is through neutralisation of RSV. To demonstrate this in vivo, serum RSV-nAbs were measured to quantify the levels of maternal RSVnAbs present at baseline and demonstrate the increase in level following administration of nirsevimab in RSV Season 1, characterise the duration of RSV-nAbs and to compare levels of endogenously produced levels in infants with confirmed RSV infection in placebo recipients. In **Study 2**, a dose-dependent increase of RSV-nAb levels was observed from baseline to Day 8 among infants who received 10, 25, or 50 mg of nirsevimab (Domachowske 2018). The RSV-nAb levels at Day 8 corresponded to more than 50-, 80-, and 110-fold increase in RSV-nAb levels vs. baseline. At least 93% of infants entering their first RSV season with samples measured for RSV-nAb in **Study 2 and 3, MELODY**, and **MEDLEY** experienced a ≥4- fold rise (conventional response criteria for several vaccines and passive immunotherapies) following administration of nirsevimab in RSV Season 1. Following administration of nirsevimab, subjects entering their first RSV Season had RSV-nAb (GMC) corresponding to an approximately >140-fold increase from baseline to Day 31 in the MELODY subjects, a >90-fold increase from baseline to Day 91 in the **Study 3** subjects (see also **Tables 76.1.1, 76.1.2, 76.3.1, 76.3.2, Appendix 2.7.2.5, Module 5.3.5.3**). In Season 1, **MEDLEY** subjects had a >300-fold increase from baseline to Day 31 (greater fold increase as had lower baseline levels vs. **MELODY)** (see also **Table 14.2.6.2, MELODY iCSR, Module 5.3.5.1; and Tables 14.2.6.1.1, 14.2.6.2.1, MEDLEY iCSR, Module 5.3.5.1**). At Day 151 in the first RSV Season, the RSV-nAb levels in infants receiving nirsevimab were still more than 50 times greater than baseline levels in **Study 3** and **MELODY,** confirming the durability of the nAb levels following a single dose. These levels are far greater than those in placebo subjects with diagnostic-confirmed RSV infections with an average increase of just 1- to 3-fold RSV-nAbs relative to baseline. At Day 361, RSV-nAb levels in placebo subjects with a diagnostic-confirmed RSV infection had maintained or showed a small increase in RSV-nAbs, but further declines were seen in placebo subjects without confirmed RSV, demonstrating their ongoing vulnerability to RSV. This may be particularly important because of the altered epidemiology of RSV during public health measures to curtail the spread of COVID-19 (discussed later).

5.1.2.2. Secondary pharmacodynamic effects

None.

5.1.3. Time course of pharmacodynamic effects

As described above.

5.1.4. Relationship between drug concentration and pharmacodynamic effects

As described above.

5.1.5. Genetic, gender and age related differences in pharmacodynamic response

As described above.

5.1.6. Pharmacodynamic interactions

ADA was measured in all the clinical studies; the findings are described in the results of each study. Overall, ADA was low, and even when ADA was detected the PK of nirsevimab was not impacted negatively and there was no safety signal of concern associated with ADA positivity.

5.2. Evaluator's overall conclusions on pharmacodynamics

Following administration of a single dose of nirsevimab in infants entering their first RSV season in **Study 2 and 3**, **MELODY** (Primary Cohort), and **MEDLEY** Season 1, dosedependent high increases in serum anti-RSV-nAB levels were demonstrated. The fold increase in nAbs was

far greater than those seen induced by RSV infection itself. Durability of these high 'protective' levels was demonstrated and would provide protective levels for the average 5 mth RSV season, supporting single dose in Season 1 of RSV. Boosting levels in RSV season 2 in those who are highly vulnerable is safe (See **MEDLEY** and **MUSIC** in **Section 7** of this report) and seem appropriate especially as the consequences of severe RSV are associated with considerable morbidity and mortality. Last, serum anti-RSV-nAb levels were correlated with nirsevimab serum conc'ns across all dose levels, confirming nirsevimab's anti-RSV-neutralising activity.
Study 3 showed a ≈70% reduction in MA RTI with 50mg single dose nirsevimab in Season 1 RSV healthy infants; there were similar findings with weight-based dosing of 50mg or 100mg nirsevimab in RSV season 1 health infants i.e. RRR in the incidence of MA RSV LRTI through 150 days post dose of 76.36%. **MEDLEY,** and **MUSIC** are ongoing studies gathering further information on the clinical efficacy of nirverimab, including in the highly vulnerable pop'n in **MUSIC**. These data are presented in greater detail in **Section 7** of this report.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

6.2. Phase II dose finding studies

Study Title: D5290C00003 A Phase 2b Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, in Healthy Preterm Infants
Study design and patient pop'n: Phase 2b, randomised, double-blind, placebo-controlled, single-dose study to determine if MEDI8897 would be efficacious in reducing MA RSV-confirmed LRTI in healthy preterm infants entering their first RSV season.
Pop'n: healthy preterm infants born between 29 wks 0 days and 34 wks 6 days gestational age (GA) who would not receive RSV prophylaxis based on the American Academy of Pediatrics (AAP) or other local or national guidelines.
Study sites: 164 sites in 23 NH countries: 136 sites in 17 countries (Belgium, Bulgaria, Canada, Czech Republic, Estonia, Finland, France, Hungary, Italy, Latvia, Lithuania, Poland, Spain, Sweden, Turkey, United Kingdom (UK), US) and 28 SH sites in 6 countries (Argentina, Australia, Brazil, Chile, New Zealand, South Africa).
Study dates: 03-Nov-2016 to 06-Dec-2018
Methods: Subjects randomised 2:1 to receive a 50 mg IM (anterolateral thigh) MEDI8897 dose (N = 1,000) or N-saline placebo (N = 500). Randomisation stratified by hemisphere and subject age at randomisation (i.e. ≤3 mths, >3 to ≤6 mths, and >6 mths). Enrolment of infants > 6 mths of age was limited to ≈500. All infants followed for ≈360 days after dosing.
RSV testing: central testing using FDA-approved and CE-marked in vitro diagnostic real-time RT-PCR assay (Lyra RSV + human metapneumovirus (hMPV) Assay, Quidel, San Diego, CA). A diagnosis of RSV LRTI required a respiratory sample positive for RSV by RT-PCR.
Clinical assessment: Protocol-specified criteria for LRTI i.e. signs of LRTI (rhonchi, rales, crackles, or wheeze on examination) AND any of the following: Increased respiratory rate at rest (age: <2 mths, ≥ 60 breaths/min; 2 to 6 mths, ≥50 breaths/min; >6 mths to 2 years, ≥40 breaths/min); Hypoxaemia (in room air - oxygen saturation <95% at altitudes ≤1,800 metres or <92% at altitudes >1,800 metres); Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for intravenous (IV) fluid).
Serum PK and ADA (using MedImmune validated assays)**:** Screening, and Days 91, 151, 361 and as needed for example PK samples were taken if subjects were hospitalised with LRTI.
Statistical Methods: 1,500 infants planned for enrollment. For subjects with multiple medically attended RSV LRTI (inpatient or outpatient), only the first occurrence used in the primary analysis. The primary efficacy analysis of the primary endpoint was performed on the Intent-to-treat (ITT) Pop'n. A Poisson regression model with robust variance (Zou) was used as the

primary efficacy analysis model to estimate the relative risk (RR) on the incidence of medically attended RSV LRTI between the MEDI8897 and the placebo gps. The model contained the term of treatment gp and age gp at randomisation and dichotomous temperate (northern and southern) hemispheres as covariates. The relative risk reduction (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 null hypothesis that the incidence of medically attended RSV LRTI between MEDI8897 and placebo gps were the same obtained from the model. Statistical significance would be achieved if the 2-sided p value was ≤0.05. RSV LRTI that occurred through 150 days post dose contributed to the primary efficacy analysis. For subjects who did not have a medically attended RSV LRTI and were not followed through 150 days post dose, their event status was imputed assuming the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation techniques. The analysis described above was also conducted on the Per-protocol (PP) Pop'n. The sample size of 1,500 subjects was necessary based on advice from the US FDA requesting that 1,000 preterm infants be exposed to MEDI8897 in this Phase 2b study. This sample size had ≈>99% power to detect 70% RRR, assuming a placebo gp medically attended RSV LRTI incidence of 8%. Power calculations based on a Poisson regression model with robust variance (Zou) comparing MEDI8897 50 mg to placebo, with 2-sided, α=0.05. The 70% RRR assumption was based on a placebo-controlled study in Native-American infants in which there was 87% relative reduction in the incidence of RSV hospitalisation (11.3% placebo; 1.5% motavizumab; p<0.001) and 71% RR in the incidence of outpatient RSV LRTI (10.0% placebo; 2.9% motavizumab; p<0.001) in infants who received motavizumab prophylaxis (O'Brien). To evaluate the risk, sample size of 1,000 subjects exposed to MEDI8897 provided a 90% probability of observing at least 1 AE if the true event rate was 0.2%; if no AEs were observed, this study provided 95% confidence that the true event rate was <0.3%.

Dosing and duration of treatment: Single 50mg IM dose of MEDI8897 or N-saline placebo IM.

Key inclusions: Healthy infants born between 29 wks 0 days and 34 wks 6 days GA (=preterm); in all countries except the EU: infants who entered their first full RSV season at the time of screening. In the EU: Infants who were ≤8 mths of age and entered their first full RSV season at the time of screening; written informed consent obtained from the subject's parent(s)/legal representative (LAR).

Key exclusions: Immunocompromised; active RSV; receipt of palivizumab or another RSV mAb or any RSV vaccine, including maternal RSV vaccination.

Primary Efficacy endpoint: Incidence of MA LRTI (inpatient and outpatient) due to RT-PCR-confirmed RSV over the duration of the 5-mth RSV season.

Secondary endpoints: Incidence of hospitalisations due to RT-PCR-confirmed RSV over the duration of the 5-mth RSV season; Safety and tolerability of MEDI8897 as assessed by the occurrence of all treatment-emergent adverse event (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse event (AE) of special interest (AESIs), and new onset chronic disease (NOCD); Single-dose MEDI8897 serum conc'ns, serum ADA.

Results: Demographics and Baseline Disease Characteristics: 1,453 subjects randomly assigned to placebo (n = 484) or MEDI8897 (n = 969). Demographic and baseline characteristics well matched between gps. The majority of subjects were White (72.2%), 52.4% were male (52.4%), mean age 3.29 mths (range, 0.1 to 11.9 mths).

Efficacy Results: Single dose of 50 mg IM MEDI8897 resulted in a RRR in the incidence of medically attended RSV-confirmed LRTI through 150 days post dose of 70.1% (95% CI: 52.3%, 81.2%) when compared to placebo (p <0.0001; **Table 7**). Similar results were seen based on the same primary analysis model in the PP Pop'n and the supporting analysis models (Poisson regression with robust variance with adjustment of follow-up time and stratified CMH test) in the ITT Pop'n. In addition, the sensitivity analysis for incidence of medically attended RSV-confirmed LRTI using different methods for missing data imputation demonstrated results similar to that of the primary analysis. RSV-confirmed LRTI was observed in 9.5% of subjects in the placebo gp and 2.6% of subjects in the MEDI8897 gp. In each gp, the incidence of RSV-confirmed LRTI was higher in the outpatient setting. In the inpatient setting, all RSV-confirmed LRTI were primary hospitalisations. In the outpatient setting, the highest incidence of RSV-confirmed LRTI was observed in the outpatient clinic. The incidence rates of medically attended

RSV-confirmed LRTI were lower in the MEDI8897 gp than the placebo gp for all age at onset categories, except for the category where subjects were ≤3 mths at randomisation and >6 mths at onset (incidence rates were similar: 0.4% in placebo gp vs. 0.6% in MEDI8897 gp). MEDI8897 demonstrated activity against both A and B subtypes. In each of the treatment gps and reporting periods, A and B subtypes accounted for similar proportions of MA RSV-confirmed LRTI. Very few RSV LRTI events occurred 150 days post dose, reflecting the end of the RSV season.

Table 7. Incidence of MA RSV-confirmed LRTI Through 150 Days Post Dose (ITT Pop'n) in Study 3

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

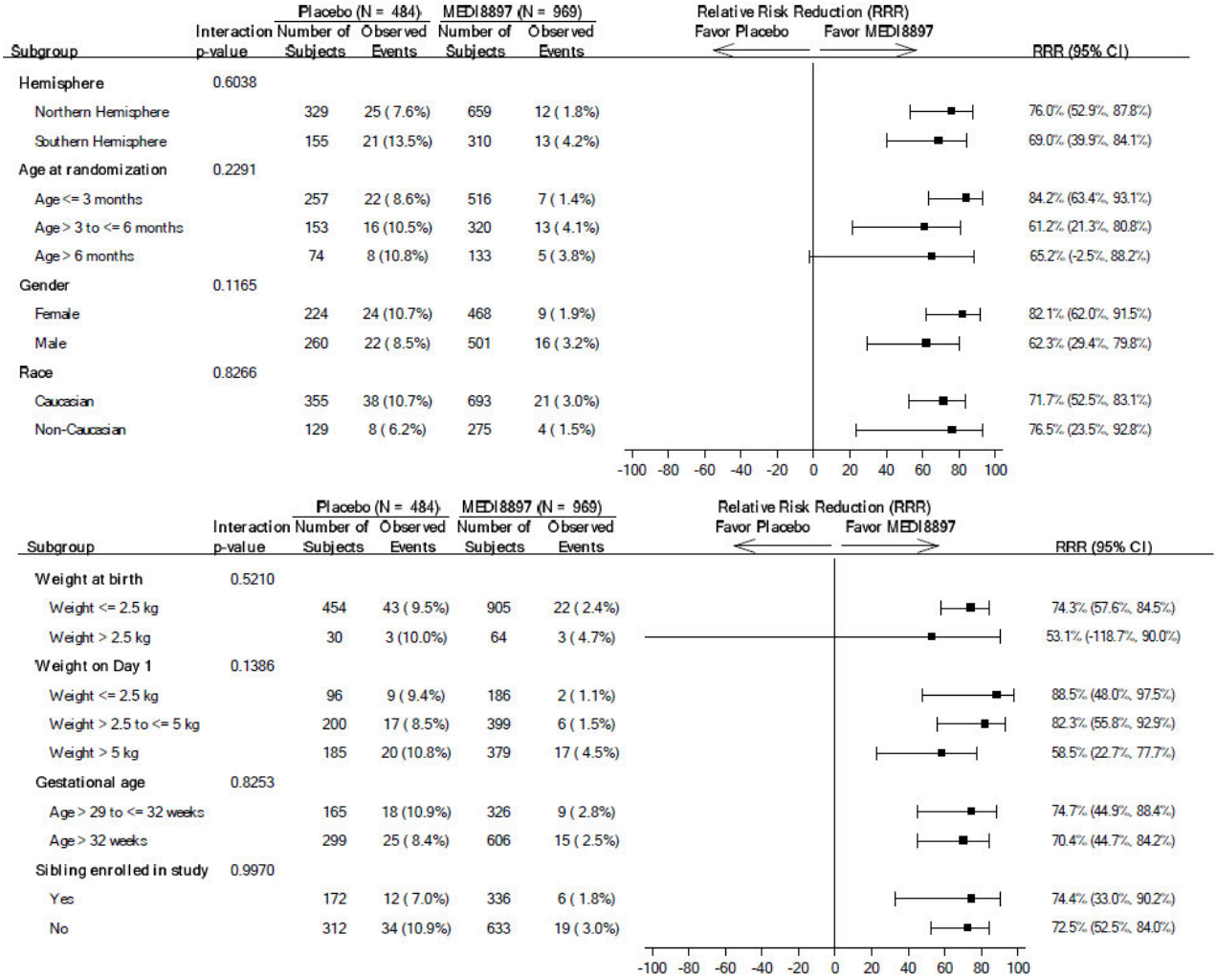
CI = confidence interval; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; NA = not applicable; RSV = respiratory syncytial virus.

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

Subgp Analysis of Primary Endpoint: Subgp analyses of the primary efficacy endpoint (incidence of MA RSV confirmed LRTI through 150 days post dose) showed consistent results for hemisphere, age at randomisation, weight at birth, weight at Day 1, GA, and siblings enrolled in the study (**Figure 1**). No statistically significant interactions were observed between each subgp and treatment and RRRs through 150 days post dose, favouring MEDI8897 vs. placebo across all subgps. While efficacy **was** demonstrated for infants >5 kg, it was **less** than that seen for the smaller-weight infants. Additional PK exposure-efficacy analyses showed that a dose of 100 mg would give similar exposures for infants ≥5 kg with a predicted improvement in efficacy (**see Appendix 16.1.13 for MEDI8897 Modeling and Simulation Analysis Report**).

PK: The serum conc'ns decayed monoexponentially beyond the Day 91 sampling timepoint without any sign of PK nonlinearity (**Table 8**). This observation highlights that the distribution phase of MEDI8897 occurs prior to Day 91 and validates nonspecific catabolism of MEDI8897 as its only elimination pathway, regardless of RSV exposure. On Day 151, 97.8% (851/833) of MEDI8897 serum conc'ns were above the targeted 90% effective conc'n threshold of 6.8 µg/mL. Additionally, due to the overlapping exposures, there was no difference in serum conc'n profiles of individuals who were ADA-positive or negative at any time during the entire follow-up period. Due to the sparse sampling, the noncompartmental analysis was performed in only 48 subjects. The estimated apparent mean (SD) half-life was 59.3 (9.6) days (**Table 9**). This is consistent with the findings of the PK studies described in **Section 19.1.1** of this report.

Figure 1. Forest Plot for Subgp Analysis for Incidence of MA RSV-confirmed LRTI (Observed) Through 150 Days Post Dose (ITT Pop'n) in Study 3



CI = confidence interval; ITT = Intent-to-treat; LRTI = lower respiratory tract infection; RRR = relative risk reduction; RSV = respiratory syncytial virus.
Source: Figure 14.2.1.15 and Table 14.2.1.10.

Table 8. Summary of MEDI8897 Serum Conc'ns by Nominal Sampling Time in Study 3

Nominal Time Point-Dose (Day)	N	Mean (SD) Serum Concentration (µg/mL)
90	883	35.9 (10.9)
150	849	18.9 (7.4)
360	771	2.1 (1.1)

SD = standard deviation.
Source: Listing 16.2.5.3

Table 9. MEDI8897 Serum PK Parameters in Study 3

Parameter	N	Mean[a] (%CV)
$AUC_{0-\infty}$ (day*µg/mL)	48	5176.3 (35.0)
CL/F (mL/day)	48	9.7 (36.1)
$t_{1/2}$ (day)	48	59.3 (9.6)

%CV = percent coefficient of variation; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; CL/F = apparent clearance; $t_{1/2}$ = half-life.

[a] Arithmetic and standard deviation was reported for half-life, geometric mean and %CV for all other parameters.

ADA: Of those with samples available, ADA was detected post baseline in 3.8% (18/469) of subjects (placebo gp) and 5.6% (52/929) (MEDI8897 gp). ADA titres ranged from 1:50 to 1:400 (placebo gp) and 1:50 to 1:6,400 (MEDI8897 gp). Post-baseline results were as follows: 0.9% (4/455) in the placebo gp and 1.2% (11/890) in the MEDI8897 gp on Day 91; 1.3% (6/445) in the placebo gp and 2.0% (17/867) in the MEDI8897 gp on Day 151; and 1.9% (8/418) in the placebo gp and 3.5% (30/847) in the MEDI8897 gp on Day 361. Of the subjects in the placebo gp who were post-baseline ADA positive, ADA targeting the YTE domain was observed in 0 of 6 subjects on Day 151 and 5 of 8 subjects (62.5%) on Day 361. One subject in the placebo gp had neutralising ADA on Day 361. In the MEDI8897 gp who were post-baseline ADA positive, ADA targeting the YTE domain was observed in 4 of 17 (23.5%) on Day 151 and 23 of 30 subjects (76.7%) on Day 361. Three MEDI8897 gp subjects (10.0%) had neutralising ADA on Day 361.
Safety: In the As-treated Pop'n, AE rates for the MEDI8897 gp were generally comparable or lower than placebo gp across the event categories. Overall, 86.8% of subjects in the placebo gp and 86.2% of subjects in the MEDI8897 gp had ≥1 AE. AEs that occurred ≤1 day post dose were observed in 2.5% of subjects in both gps. In comparison to the placebo gp, the MEDI8897 gp had a lower incidence of AEs occurring ≤7 days post dose (15.2% vs. 12.5%, respectively), AEs ≥Grade 3 in severity (12.5% vs 8.0%, respectively), and SAEs (16.9% vs 11.2%, respectively).

Five deaths (3 placebo gp; 2 in MEDI8897 gp) were reported during the study through Day 361. One additional subject in the placebo gp died on Day 367. None of these deaths were considered related to investigational product (IP) by the investigator. Overall, the incidence of TRAEs (placebo 2.1%, MEDI8897 2.3%), AESIs (hypersensitivity, immune complex disease, and thrombocytopaenia; placebo 0.6%, MEDI8897 0.5%); skin hypersensitivity reactions (placebo 0.6%, MEDI8897 0.5%), and NOCDs (placebo 0.8%, MEDI8897 0.4%) was low and generally comparable between the gps. Overall, there was no notable difference between the placebo and MEDI8897 gps when AEs were analysed by either post-baseline positive ADA (88.9% and 94.2%, respectively) or post-baseline negative ADA (86.8% and 85.7%, respectively

6.3. Phase III pivotal studies investigating more than one dose regimen

See **Section 7**.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

Study 3 an international trial conducted across both hemispheres, demonstrated a RRR of the incidence in MA RSV LRTI in this preterm infant pop'n in RSV Season 1 given a single IM dose of 50mg of 70.1% (95% CI: 52.3%, 81.2%) (p <0.0001) through 150 days post dose. However, as demonstrated in the prespecified subgp analysis of the primary endpoint by weight at dosing there was a significantly **lower efficacy** in the infants weighing >5 kg, with RRR of incident MA RSV LRTI through 150 days post dose of 58.5% for infants >5 kg vs. >80% for infants ≤5 kg. Based on an exposure-response analysis for the primary endpoint with AUC (derived using individual CL at baseline) quartiles as the exposure metric, a serum AUC above the first quartile (Q1) was determined as the clinically efficacious target exposure to provide protection against MA RSV LRTI throughout the typical 5-mth RSV season. (Of note, the quartiles were updated based on the final **Study 3** PK dataset resulting in Q1 = 12.8 mg day/mL). Moving forward into **Studies 4, 5 and 8** (described in **Section 7** below), a 100 mg dose was proposed to achieve the target exposure in infants weighing ≥5 kg in Season 1, and a 200 mg dose proposed in Season 2, based on the expected body weight range in older infants experiencing their second RSV season. The dosing regimen was predicted to result in at least 80% of the pop'n achieving exposures above the target exposure. Nirsevimab 50 mg single dose was well tolerated in this infant pop'n.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

Pivotal:
- **D5290C00003 (study 3)**: Phase IIb, randomised, double-blind, placebo-controlled, (efficacy, safety, PK, and ADA) (see above in **Section 6**)
- **D5290C00004 (study 4, MELODY)**: Phase III, randomised, double-blind, placebo-controlled (efficacy, safety, PK, and ADA).
- D5290C00005 (study 5, MEDLEY): Phase II/III, randomised, double-blind, palivizumab-controlled (safety, descriptive efficacy, PK, and ADA).
Supportive: D5290C00008 (study 6, MUSIC): Phase II, Open-label, uncontrolled, single-dose study (safety, descriptive efficacy, PK, and ADA)

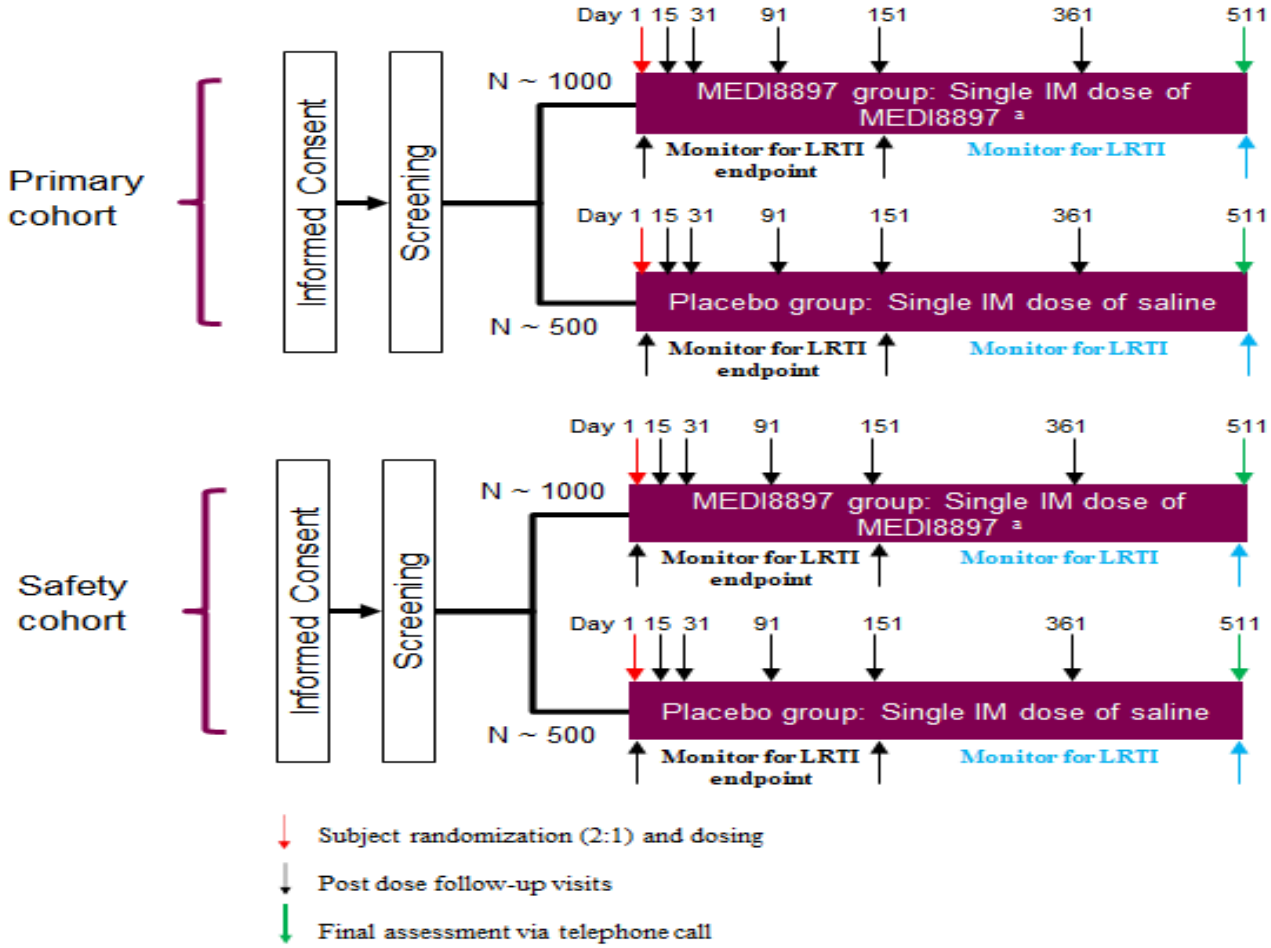
7.2. Pivotal or main efficacy studies

7.2.1. Study ID - D5290C00004 (MELODY): 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

7.2.1.1. Study design, objectives, locations and dates

Design: Phase III, multicentre, randomised, double-blind, placebo-controlled, single-dose study to determine if nirsevimab will prevent MA RSV LRTI in late preterm and term infants born ≥35 wks 0 days GA and entering their first RSV season. **Figure 2** details the overall design.
Objectives: See below in **Table 10.**
Blood samples for assessment of PK, ADA, anti-RSV nAb, and RSV serology were collected through 360 days post dose according to the scheduled timepoints (see also **Appendix 16.1.1, Section 4.2.2 of the Global and local CSPs**). Additional bloods collected if subjects hospitalised with LRTI or any respiratory infection within ≈2 days following hospitalisation. PK in serum measured using a validated ligand binding assay. ADA assessments conducted following a tiered approach (screen, confirm, titre) using a validated ligand binding assay. NAbs and antibodies against the YTE-substitution was tested in all ADA positive samples using validated ligand binding assays. The anti-RSV nAb evaluations were performed based on a previously described assay (Shambaugh). RSV serology analysed using a described assay (Maifeld).
Locations: 160 centres in 21 countries.
Dates: First subject enrolled: 23-Jul-2019; last visit has not yet occurred. Data cut offs: The analyses presented in this report are based on: a data cut-off date of 11-Mar-2021 (data lock 14-Apr-2021) for the Primary Analysis complete to Day 361; a data cut-off date of 09-Aug-2021 (data lock 10-Sep-2021) for the Primary Analysis complete to Day 511; a data cut-off date of 31-Mar-2022 (data lock 29-Apr-2022) for the Safety Analysis complete to Day 151.
Publications: Hammitt

Figure 2. Flow Chart of Study Design of MELODY



Footnote: [a] MEDI8897 = nirsevimab. Primary Cohort: randomised subjects from the Primary Cohort completed follow-up through Day 511. Safety Cohort: randomised subjects from the Safety Cohort completed follow-up through at least Day 151. .

7.2.1.2. Inclusion and exclusion criteria

Inclusion criteria: 1. Healthy infants in their first year of life and born ≥35 wks 0 days GA (infants with an underlying illness such as CF or Down syndrome with no other risk factors were eligible) (Note: In Japan, this inclusion criterion was healthy infants born ≥36 wks 0 days GA and excluded Down syndrome); 2. Infants who were entering their first RSV season at the time of screening; 3. Written informed consent and any locally required authorisation was obtained from the subject's parent(s)/LAR prior to performing any protocol-related procedures, including screening; 4. Subject's parent(s)/LAR able to understand and comply with the requirements of the protocol as judged by the investigator; 5. Subject available to complete the follow-up, i.e. 17 mths after receipt of study drug.
Exclusion criteria: 1. Met the national or other local criteria to receive commercial palivizumab**;** 2. Any fever (≥100.4°F [≥38.0°C]) or acute illness within 7 days prior to randomisation**;** 3. Any history of LRTI or active LRTI prior to, or at the time of, randomisation**;** 4. Known history of RSV infection or active RSV infection prior to, or at the time of randomisation; 5. Any drug therapy (chronic/other) within 7 days prior to randomisation or expected receipt during the study with the exception of: a) multivitamins and iron; b) infrequent use of over-the-counter (OTC) medications for the systemic treatment of common childhood symptoms could be permitted according to the judgment of the investigator**;** 6. Any current or expected receipt of immunosuppressive agents including steroids (except for the use of topical steroids according to the judgment of the investigator)**;** 7. History of receipt of blood, blood products, or immunoglobulin products, or expected receipt through the duration of the study**;** 8. Receipt of any investigational drug**;** 9. Known renal impairment**;** 10. Known hepatic dysfunction including known or suspected active or chronic hepatitis infection**;** 11. History of CLD/bronchopulmonary dysplasia**;** 12. Clinically significant congenital anomaly of the respiratory tract**;** 13. Chronic seizure or evolving or unstable neurologic disorder**;** 14. CHD, except for children with uncomplicated CHD (e.g. patent ductus arteriosus, small septal defect)**;** 15. Prior history of a suspected or actual acute life-threatening event**;** 16. Known immunodeficiency, including HIV**;** 17. Mother with HIV infection (unless the child was proven not infected)**;** 18. Any known allergy, including to immunoglobulin products, or history of allergic reaction**;** 19. Receipt of palivizumab or another RSV mAb or any RSV vaccine, including maternal RSV vaccination (Note: Exclusion criterion not applicable in Japan); 20. Receipt of any monoclonal or polyclonal antibody**;** 21. Any condition that, in the opinion of the investigator, would interfere with evaluation of the IP or

interpretation of subject safety or study results; 22. Concurrent enrolment in another interventional study; 23. Children of employees of the Sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals.

7.2.1.3. Study treatments

Nirsevimab: Single IM dose 50 mg (<5 kg weight) or 100 mg (if ≥5 kg weight). Batch nos. P65704LA, P65705LA, P65706LA. **Placebo**: Commercially available 0.9% (w/v) saline.

7.2.1.4. Efficacy variables and outcomes

Table 10. Objectives and Endpoints in MELODY

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 * 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

* Subjects in Japan were ≥ 36 weeks 0 days gestational age.

The protocol defined objective criteria for a MA LRTI i.e. signs of LRTI = documented at least one physical exam finding of rhonchi, rales, crackles, or wheeze **AND** at least one of the following: Increased respiratory rate at rest (age <2 mths, ≥60 breaths/min; age 2 to 6 mths, ≥50 breaths/min; age >6 mths, ≥40 breaths/min) **OR** hypoxaemia (room air: oxygen saturation <95% at altitudes ≤1800 metres or <92% at altitudes >1800 metres), **OR** Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) **OR** dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid). A diagnosis of RSV LRTI required a respiratory sample to test positive for RSV by the central laboratory (lab) RT-PCR.

7.2.1.5. Randomisation and blinding methods

Interactive web response system (IWRS) used for randomisation. This is a double-blind study in which sites are using commercially available N-saline as the placebo. MEDI8897 and placebo are visually indistinguishable once in syringes. Neither the subject/LAR nor site staff involved in the treatment or clinical evaluation will be aware of the treatment received. The study is to maintain a double-blind setting until data base lock (DBL) for the Primary and Safety Analyses. When the primary DBL occurred, only unblinded data from the Primary Cohort were transferred to the Sponsor for analysis. The unblinding data from the Safety Cohort were not transferred to the Sponsor until the DBL for Safety Analysis. The original plan was that the site

personnel, subjects, and the study team members involved in advice or decisions involving study subjects or day-to-day interactions with the site would remain blinded until the end of the study (all subjects have completed the Day 511 visit) to ensure study integrity maintained.

7.2.1.6. Analysis populations

Table 11. Analysis Pop'ns in MELODY

Population	Description
Intent-to-treat population (ITT)	Subjects who were randomised were included in the ITT population (including both Primary and Safety Cohorts); in this population data were analysed according to their randomised treatment group.
Intent-to-treat population 1 (ITT1)	Subjects in the ITT population and from the Primary Cohort.
Intent-to-treat population 2 (ITT2)	Subjects in the ITT population and from the Safety Cohort.
As-treated population (AT)	Subjects who were randomised and received any investigational product were included in the AT population (including both Primary and Safety Cohorts); in this population, data were analysed according to the treatment they actually received.
As-treated population 1 (AT1)	Subjects in the AT population and from the Primary Cohort.
As-treated population 2 (AT2)	Subjects in the AT population and from the Safety Cohort.
Per-protocol population (PP)	The PP population included subjects in the ITT1 population who received the correct dose of randomised treatment and who did not have a serious protocol deviation. Further details are provided in the SAP (see Appendix 16.1.9).

Note: ITT1 and ITT2 were derived and combined for MELODY (All Subjects) analyses with all Primary Cohort data and Safety Cohort data (up to Day 151 only), respectively.

7.2.1.7. Sample size

The study was originally designed to analyse the primary endpoint on the full enrolment of ≈3000 infants. However, the impact of the COVID-19 pandemic on RSV circulation led to a protocol amendment, in consultation with regulatory authorities (Type B meeting, Dec 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. As a result, the study 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 IM dose of nirsevimab (50 mg for infants <5 kg or 100 mg for infants ≥5 kg) or placebo. Enrolment in the Primary Cohort is complete and included subjects from the NH 2019/2020 and SH 2020 enrolment seasons (South Africa the only SH country). One additional subject was enrolled from Japan in the NH 2020/2021 season, prior to pausing the study due to the COVID-19 pandemic. Enrolment in the Safety Cohort is complete and included subjects from the NH 2020/2021and SH 2021 enrolment seasons.

7.2.1.8. Statistical methods

Primary Efficacy Analysis: The incidence of RSV LRTI (inpatient and outpatient) during 5 mths of the RSV season will be based on RSV test results and objective clinical LRTI criteria and is presented by treatment gp. For subjects with multiple MA RSV LRTI events, only the first occurrence used in the primary analysis. The primary efficacy analysis is conducted on the ITT Pop'n. RSV LRTI occuring through 150 days post dose will contribute to the primary efficacy analysis. For subjects who do not have a MA RSV LRTI and are not followed through 150 days post dose, their event status will be imputed assuming the observed placebo RSV LRTI rate conditional on stratification factors using multiple imputation techniques as described in the Statistical Analysis Plan (SAP). A Poisson regression model with robust variance will be used as

the primary efficacy analysis model to compare the incidence of MA RSV LRTI between MEDI8897 and placebo, including treatment gp, age at the time of randomisation (i.e. ≤3 mths, >3 to ≤6 mths, >6 mths), and dichotomous temperate NH and SH as covariates. In addition, the 2-sided p-value and corresponding 2-sided 95% CI on the RR will be provided from the model. RRR is defined as (1 - Pn/Ps) where Pn is the incidence of RSV LRTI through 150 days post dose in the MEDI8897 gp and Ps is the incidence of RSV LRTI through 150 days post dose in the placebo gp generated by the model. Statistical significance will be achieved if the 2-sided p-value is ≤0.05.

Additional Analyses of the Primary Endpoint: A Cochran-Mantel-Haenszel approach stratified by hemisphere and age gp at time of randomisation will be used to compare the incidence of RSV LRTI through 150 days post dose between treatment gps as a secondary analysis for the primary endpoint. In addition, a time-to-event analysis assessing time to first RSV LRTI may be performed as a supplementary analysis. An analysis may also include all RSV positive LRTI endpoints, using results from either the central lab or local lab. Different approaches to handle missing data may be considered for supplementary analyses. Additional analyses may be performed to adjust duration of efficacy follow-up and to assess the efficacy within subgps. These analyses will be described in the SAP.

Secondary Endpoint Analyses: Efficacy: The incidence of RSV hospitalisation through 150 days post dose will be presented by treatment gp. Similar methods as described above for the primary efficacy endpoint will be used to assess efficacy on RSV hospitalisation.

Safety: Occurrence of TEAEs and TESAEs. AE graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) where applicable for paediatric assessments. AE will be coded by Medical Dictionary for Regulatory Activities (MedDRA) and the type, incidence, severity, and relationship to IP summarised by treatment gp. Other safety assessments include: AESIs (i.e. hypersensitivity (including anaphylaxis), thrombocytopaenia, and immune complex disease) and NOCDs.

PK: Individual MEDI8897 serum conc'n data will be tabulated by treatment gp along with descriptive statistics. PK parameters will be estimated using non-compartmental analysis, data permitting. **ADA:** Incidence will be assessed and summarised by nos. and percentage positive by treatment gp. Impact of ADA on PK, efficacy, and safety will be assessed.

Subgp Analyses of the Primary Endpoint: Treatment-by-subgp interaction will be tested using the Poisson regression with robust variance model with the terms of treatment, age gp, hemisphere, subgp, and treatment-by-subgp interaction. If this full model does not achieve convergence, a reduced model of treatment, subgp, and treatment-by-subgp interaction will be used. Significant treatment-by-subgp interaction is judged at the significance level of 0.10. Within each level of a subgp, the RRR and its corresponding 95% CI will be estimated using a Poisson regression model with robust variance with the term of treatment. A forest plot of the RRR and the 95% CI will be presented. If the Poisson regression model does not converge for any stratum of a subgp, the exact conditional method based on the nos. of RSV LRTIs (Breslow and Day) will be used as the analytical model to generate the RRR and its corresponding CI for all subgp strata. The subgp analysis will be conducted for the following subgps on the ITT Pop'n: Hemisphere; age at randomisation stratum; gender; race (White vs. other races); weight at birth (≤2.5 kg, >2.5 kg to <5 kg, ≥5 kg); weight on Day 1 (<5 kg, ≥5 kg); sibling also participating in the study (yes/no).

Sensitivity Analyses of the Primary Endpoint: Impact of COVID-19 Pandemic: The COVID-19 pandemic has posed challenges in study conduct (including performing scheduled visits, and sample collections). **As detailed in the SAP, Section 3.10; see Appendix 16.1.9**: 3 sensitivity analyses of the primary endpoint were conducted for ITT1.

Original plan: MELODY will enroll ≈3,000 subjects of whom ≈2,000 will receive MEDI8897 and 1,000 will receive placebo. The 2,000 subjects to be dosed with MEDI8897 in **MELODY**, together with the 968 subjects dosed with MEDI8897 in **Study 3** and the 1,000 subjects to be dosed with MEDI8897 in **Study 5**, will contribute to a prelicensure safety database of ≈ 4,000 infants exposed to MEDI8897. To evaluate risk, a sample size of 2,000 exposed to MEDI8897 in this

study will provide a >99% probability of observing at least one AE if the true event rate is 0.3%; if no AEs are observed, this study provides 98% confidence that the true event rate is <0.2%. The primary and secondary efficacy hypotheses will be assessed in the primary analysis by a hierarchical order. That is, the secondary hypothesis will be tested at a significance level of 0.05 only if the treatment effect on the primary efficacy endpoint is demonstrated at the significance level of 2-sided 0.05. More specifically, after the significance of the primary efficacy endpoint is demonstrated, the secondary efficacy endpoint will first be tested from pooling all ITT subjects from **Study 3** and **MELODY**. If the significance of the pooled efficacy based on pooling all subjects from Phase 2b and Phase 3 is demonstrated (at 2-sided 0.05), the secondary efficacy endpoint will be further tested from pooling the 860 subjects weighing <5 kg on Day 1 (i.e. 290 placebo subjects and 570 MEDI8897subjects) in **Study 3** and all subjects in **MELODY**. If the significance of the pooled efficacy based on pooling the subjects weighing <5 kg from Phase 2b and all Phase 3 subjects is demonstrated (at 2-sided 0.05) again, the secondary efficacy endpoint will be tested using subjects from **MELODY** (this study) alone. With that, the overall Type I error is controlled at 0.05. Therefore, no further multiplicity adjustment is necessary.

7.2.1.9. Participant flow

Primary Cohort: 1626 subjects screened, with 1490 subjects randomly assigned to nirsevimab (n = 994) or placebo (n = 496). Of the 1490 randomised subjects, 987 in the nirsevimab gp and 491 in the placebo gp were dosed. Twelve subjects (7 nirsevimab and 5 placebo) did not receive any IP. The majority completed the Day 151 follow-up (977 subjects [98.3%] nirsevimab; 488 subjects [98.4%] placebo). 89 nirsevimab subjects (9.0%) and 43 placebo subjects (8.7%) completed the study as of clinical DCO (11-Mar-2021). The majority of early discontinuations in both gps resulted from withdrawal by parent/LAR (n = 34) and lost to follow-up (n = 12).
MELODY (All Subjects): 3319 subjects screened and 3012 randomly assigned to nirsevimab (n = 2009) or placebo (n = 1003). Of the 3012 randomised subjects, 1998 in the nirsevimab gp and 996 in the placebo gp were dosed. Eighteen subjects (11 nirsevimab and 7 placebo) did not receive any IP. The majority of subjects completed the Day 151 follow-up (1886 subjects [93.9%] nirsevimab; 938 subjects [93.5%] placebo). 907 subjects (45.1%) (nirsevimab) and 450 (44.9%) placebo subjects had completed the study as of clinical DCO (31-Mar-2022). The majority of early discontinuations in both gps resulted from lost to follow-up (n = 68) and withdrawal by parent/LAR (n = 65).

7.2.1.10. Major protocol violations/deviations

4.1% had an important protocol deviation (3.8% nirsevimab gp; 4.6% placebo gp), these did not affect the interpretation of study results. **COVID-19 disruptions for the Primary Cohort**: 48.1% overall had at least 1 disruption due to COVID-19, only 9.3% of subjects in the NH had at least 1 disruption due to COVID-19 through 150 days post dose. The important protocol deviations due to the COVID-19 pandemic were not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of the results.

7.2.1.11. Baseline data

Demographic and Baseline Characteristics: MELODY (Primary Cohort) For the ITT1 Pop'n demographic and baseline characteristics were similar between the gps gps. Overall, 53.5% of subjects were White, 89.8% not Hispanic or Latino, and 51.6% were male. Median age at randomisation was 2.60 mths (range, 0.03 to 11.10 mths). Most subjects had a birth weight of >2.5 kg (85.4% nirsevimab gp; 82.3% placebo gp) and were term infants with gestational age ≥37 wks (86.7% nirsevimab gp; 84.6% placebo gp). 3 subjects only in the nirsevimab gp (0.3%) had Down syndrome. One placebo gp subject (0.2%) had CF.
Demographic and Baseline Characteristics: MELODY (All Subjects): For the overall ITT Pop'n, demographic and baseline characteristics were similar. Overall, 52.9% were White, 66.3% not Hispanic or Latino, and 52.3% were male. Median age at randomisation was 2.53 mths (range, 0.00 to 14.00 mths). Most had a birth weight of >2.5 kg (86.5% nirsevimab gp;

86.0% placebo gp) and were term infants with gestational age ≥37 wks (88.1% nirsevimab gp; 87.8% placebo gp). 4 nirsevimab gp subjects (0.2%) had Down syndrome; 3 nirsevimab gp subjects (0.1%), and 1 placebo gp subject (0.1%) had CF.

7.2.1.12. Results for the primary efficacy outcome

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%) vs. placebo (p<0.0001). 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 the Primary Analysis. The sensitivity analyses, to assess the impact of the COVID-19 pandemic, 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 12**).

Table 12. Incidence of MA RSV LRTI Through 150 Days Post Dose in MELODY

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

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

7.2.1.13. Results for other efficacy outcomes

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 13**). 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 13**). Similar results 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**, i.e. 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%) vs. (nominal p=0.0002; **Table 13**).

Table 13. Incidence of MA RSV LRTI with Hospitalisation Through 150 Days Post Dose in MELODY

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 versus placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including study as covariate for pooled studies) obtained after missing data imputation.

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

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%) vs. (p<0.0001). The results of the exploratory analysis on MA RSV LRTI (very severe) in **MELODY (All Subjects)** were consistent with the **MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool**, i.e. 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%) vs. placebo (nominal p=0.0005).

PK: Mean serum conc'ns of nirsevimab, administered as a single fixed IM dose (50 mg for <5 kg weight on Day 1, 100 mg for ≥5 kg weight on Day 1), decreased monoexponentially beyond the Day 31 sampling time point without any evidence of PK nonlinearity. Mean nirsevimab conc'ns similar in infants in the ≥5 kg weight gp compared with the <5 kg weight gp, with substantial overlap in nirsevimab serum concn's between the 2 weight gps. **Immunogenicity:** ADA was detected post-baseline in 4.6% (89/1935) of nirsevimab gp subjects and in 0.7% (7/958) of placebo gp subjects. Median titres were generally low; there was no apparent effect of ADA on efficacy or PK or safety through 150 days post dose.

Safety results: Nirsevimab was well tolerated. Similar types and frequencies of TEAEs were reported in both the nirsevimab and placebo gps. Overall, 83.7% of nirsevimab gp subjects and 81.8% of placebo gp subjects had at least one AE. The most common AEs (>10% of subjects in any treatment gp) reported with nirsevimab (vs. placebo) were URTI (29.4% vs. 28.5%), nasopharyngitis (20.4% vs. 21.5%), pyrexia (12.4% vs. 10.3%), and dermatitis diaper (nappy)

(10.5% vs. 9.2%). The majority of AEs were Grade 1 (61.9% of nirsevimab vs. 57.1% placebo) or Grade 2 (18.8% nirsevimab vs. 20.9% placebo) in severity. AEs of ≥Grade 3 severity were reported in 61 subjects (3.1%) in the nirsevimab gp and 38 subjects (3.8%) in the placebo gp. The most common Grade 3 AEs reported with nirsevimab vs. placebo were bronchiolitis (0.5% vs. 0.8%), RSV bronchiolitis (0.2% vs. 0.5%), bronchitis (0.1% vs. 0.3%), pneumonia (0.3% vs. 0.1%), and gastroenteritis (0.2% vs. 0.0%). Grade 4 or 5 events occurred in ≤1% of subjects in either gp. Similar incidence of AEs considered IP-related by the investigator in the nirsevimab (1.3% of subjects) and placebo gps (1.5% of subjects). Irritability was the most common TRAE reported, occurring in 4 nirsevimab subjects (0.2%) and 3 placebo subjects (0.3%).
AESI and NOCD: 4 AESIs based on investigator assessment (all in the nirsevimab gp), all were assessed as skin hypersensitivity events and considered IP-related; none had ADA detectable post baseline. TE NOCDs were reported in 3 nirsevimab gp subjects (0.2%) and 2 placebo gp subjects (0.2%). None were considered treatment-related. TE skin reactions considered to be IP-related were reported in 12 nirsevimab gp subjects (0.6%) (onset ≤1 to ≤14 days post dose) and 3 placebo gp subjects (0.3%) (onset ≤3 to ≤14 days post dose). No apparent impact of ADA on safety throughout the study.
Four deaths, all in the nirsevimab gp, were reported through 360 days post dose: 2 due to gastroenteritis; 1 due to skull base fracture; 1 due to unknown cause occurring on Day 140 following dosing with 50 mg nirsevimab on Day 1. No deaths were considered IP-related. There were two non-treatment emergent deaths. One death (due to a road traffic accident) occurred in the nirsevimab gp after the Day 361 reporting period, on Day 440, and one death (meningitis streptococcal) in a subject randomised but never dosed. The proportion of subjects with at least one SAE was similar between the nirsevimab and placebo gps (6.3% vs. 7.4%). Serious and/or ≥Grade 3 severity AEs were reported in 132 subjects (6.6%) in the nirsevimab gp and 76 subjects (7.6%) in the placebo gp. The most common (>0.5% of subjects in either treatment gp) SAEs in the nirsevimab gp compared with the placebo gp were bronchiolitis (1.2% vs. 1.7%), gastroenteritis (0.6% vs. 0.3%), pneumonia (0.5% vs. 0.5%). One SAE in the placebo gp (fever neonatal) was considered treatment-related by the investigator.

7.2.1.14. Evaluator commentary

Despite the challenges posed by the COVID-19 pandemic, and the amended sample size, the primary objective based on the Primary Cohort was met. In term and late preterm infants ≥35 wGA (**MELODY [Primary Cohort]),** nirsevimab demonstrated statistically significant clinical efficacy (RRR 74.5%; 95% CI 49.6%, 87.1%; p<0.0001) against the primary endpoint MA RSV LRTI. Results were consistent in the exploratory analysis in **MELODY (All Subjects)** with efficacy against MA RSV LRTI (RRR 76.4%; 95% CI 62.3%, 85.2%) similar to the Primary Cohort. Pooled analyses (multiplicity-controlled) were prespecified to estimate the efficacy of nirsevimab in subjects who received the proposed dose across the target pop'n 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, an RRR of 76.8% (95% CI: 49.4 to 89.4) was observed. Efficacy against the exploratory endpoint MA very severe RSV LRTI 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).** Serum conc'ns declined in a linear fashion after 31 days post dose in all subjects, with a substantial overlap in conc'ns between weight gps. Safety analyses showed that nirsevimab was safe and well tolerated.

7.2.2. Study ID D5290C00005: 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)

7.2.2.1. Study design, objectives, locations and dates

Although this trial's focus is safety, **descriptive efficacy, PK and ADA** are also key secondary endpoints, hence the rationale for including it in **Section 7** of this report.
Design: **MEDLEY** is a pivotal Phase 2/3 randomised, double-blind, palivizumab-controlled study to evaluate the safety, PK, ADA response, and descriptive efficacy for MEDI8897 in high-risk infants eligible to receive palivizumab when entering their first or second RSV season (Season 1 or Season 2, respectively). ≈900 palivizumab-eligible infants entering their first RSV season will be enrolled into one of 2 cohorts: (1) preterm cohort, including ≈600 preterm infants (≤35 wks GA without CLD/CHD, or (2) CLD/CHD cohort, including ≈300 infants with CLD of prematurity or haemodynamically significant CHD. Minimum of 100 infants with haemodynamically significant CHD to be enrolled. Within each cohort, randomisation stratified by Hemisphere and subject age at Season 1 randomisation (≤3 mths, >3 to ≤6 mths, >6 mths). **Figure 3** details the overall design.
Objectives: See below in **Table 14.** Blood samples for PK, ADA, anti-RSV nAb, RSV serology collected through 360 days post dose according to the scheduled timepoints. Blood samples also collected from subjects hospitalised with LRTI/any respiratory infection within ≈2 days following hospitalisation.
PK evaluations: PK of MEDI8897 and palivizumab measured utilising validated assays. **ADA**. Evaluation performed using validated immunoassays. Tiered analyses will be performed to include screening, confirmatory, and titre assay components, and the positive-negative cut points will be statistically determined from drug-naive validation samples. Samples will be utilised for further characterisation of the ADA response, including ADA to the YTE domain on MEDI8897 and assessment of nAb to MEDI8897 or palivizumab.
Anti-RSV nAB evaluations: Analyses performed using an RSV nAB assay previously described for serum samples (Shambaugh).
RSV Serology: Blood samples collected to measure RSV antigen-specific antibody levels in serum; evaluations performed using a validated immunoassay similar as described (Maifeld).

In Season 1 or Season 2, subjects in the CLD/CHD cohort who undergo cardiac surgery with cardiopulmonary bypass after receipt of Dose 1 but prior to receipt of Dose 5 will receive a replacement dose of the study drug they received for Dose 1 immediately following the surgery when determined by the physician to be medically stable for an IM injection. Any subsequent doses of study drug will continue to be given as per the protocol-specified dosing schedule. Subjects in the preterm cohort will be followed through 1 yr after Season 1/Dose 1, and subjects in the CLD/CHD cohort will be followed through 1 yr after Season 2/Dose 1. Subjects in the CLD/CHD cohort who receive a replacement dose in Season 2 will be followed through 1 yr after the last replacement dose. Subjects will be monitored throughout the study for LRTI. All subjects seeking medical attention for a respiratory illness will be evaluated for LRTI, including protocoldefined medically attended RSV LRTI. All subjects evaluated for LRTI will have respiratory samples obtained and tested centrally for RSV using the FDA-cleared and *Conformité Européenne* or European Conformity-marked in vitro diagnostic real-time RT-PCR assay. Blood samples collected for PK, ADA, and RSV nAb and RSV serology at Day 1, 31 (pre-dose), 151, 361, and as needed when presenting with a LRTI. In addition to the clinical assessment of LRTI, there are protocol definitions using objective criteria for the determination of a MA LRTI **for subjects with no underlying lung disease** (i.e. signs of LRTI =at least one physical examination finding of rhonchi, rales, crackles, or wheeze **AND** at least one of the following clinical signs**:** Increased respiratory rate at rest (age: <2 mths, ≥60 breaths/min; 2 to 6 mths, ≥50 breaths/min; >6 mths, ≥40 breaths/min), **OR** hypoxaemia (in room air: oxygen saturation <95% at altitudes ≤1,800

metres or <92% at altitudes >1,800 metres), **OR** Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluids); **for subjects with underlying lung disease (CLD or CHD)** (i.e. signs of LRTI=at least one new or worsened physical examination finding of rhonchi, rales, crackles, or wheeze **AND** at least one of the following clinical signs: Increase in baseline respiratory rate by ≥20% at rest and that rate is greater than the age-based criteria established for children with no underlying lung disease (age: <2 mths, ≥60 breaths/min; 2 to 6 mths, ≥50 breaths/min; >6 mths, ≥40 breaths/min), **OR** Hypoxaemia (O2 saturation <95% in room air or O2 saturation drop of 5 percentage points from baseline in children with baseline O2 saturation <95% in room air, or acute documented need for supplemental O2 or increased O2 requirement compared with baseline), **OR** Clinical signs of severe respiratory disease (e.g. acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, intercostal, subcostal or supraclavicular retractions, grunting) or dehydration secondary to inadequate oral intake due to respiratory distress (need for IV fluid), **OR** Prescription of new or increased dose of medications including bronchodilators, steroids, diuretics, cardiac medications.

Locations: Season 1 (and 2) subjects dosed at 126 (58) centres in 25 (18) countries.

Dates: First subject enrolled 30-Jul-2019; last visit has not yet occurred

Table 14. Objectives and endpoints in MEDLEY

Objective	Endpoint
Primary	
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
Secondary	
To evaluate serum concentrations of nirsevimab and palivizumab	• Nirsevimab and palivizumab serum concentrations • Summary of nirsevimab serum concentrations
To evaluate ADA responses to nirsevimab and to palivizumab in serum	Incidence of ADA to nirsevimab and palivizumab in serum
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

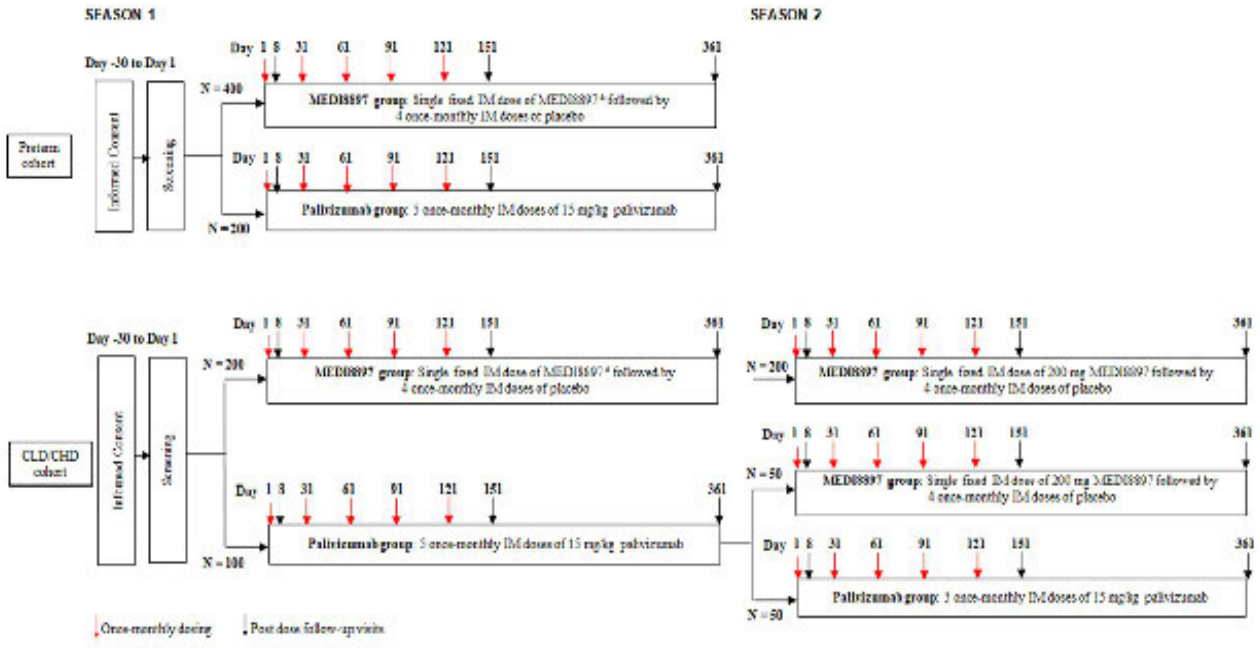
Protocol amendment:

Table 15. MEDLEY VERSION OF PROTOCOL OR PROTOCOL AMENDMENTS

Global Document Name	Version No	Version Date
First final version of the protocol prior to any amendments	1.0	05 Apr 2019
Protocol Amendment 1	2.0	31 Mar 2021
Local Document Name		
Country Name: European Union	**Version No**	**Version Date**
Local amendment 1	1.0	05 Apr 2019
Local amendment 2	1.0	06 Jun 2019
Local amendment 3	2.0	13 Apr 2021
Country Name: Japan	**Version No**	**Version Date**
Local amendment 1	1.0	5 Apr 2019
Local amendment 2	1.0	21 May 2019
Local amendment 3	2.0	13 Apr 2021

Amendment 1 (31-Mar-2021): Overall Rationale for the Amendment: The principal reason for this amendment was to update the sample size for target enrollment, introduce a primary analysis and Season 2 analysis to allow earlier assessment of Season 1 and Season 2 data, respectively, and add a description about the process to safeguard the blind.
Publication: Domachowske 2022.

Figure 3. MEDLEY Study Flow Diagram



ADA = anti-drug antibody; CHD = congenital heart disease; CLD = chronic lung disease; IM = intramuscular; PK = pharmacokinetic.
SEASON 1: Randomization for Season 1 Day 1, 2:1 MEDI8897 or palivizumab group
SEASON 2 (CLD/CHD cohort only): Randomization for Season 2 Day 1: Subjects who were randomized in Season 1 to receive MEDI8897 will receive MEDI8897 in Season 2. Subjects who were randomized to receive palivizumab in Season 1 will receive MEDI8897 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 will be collected during both seasons from all subjects hospitalized for a respiratory infection, and before and after cardiac surgery with cardiopulmonary bypass for subjects with CHD requiring a replacement dose of study drug.
Safety assessments will be performed through Day 361 for each respective season.
* In the MEDI8897 group Season 1, dose level will be stratified by body weight at time of dosing; subjects will receive 50 mg MEDI8897 if < 5 kg or 100 mg MEDI8897 if ≥ 5 kg.

Inclusion and exclusion criteria: **Inclusion Criteria:** 1. For the preterm cohort (excluding subjects with CLD or haemodynamically significant CHD): preterm infants in their first year of life and born ≤35 wks 0 days GA eligible to receive palivizumab in accordance with national or local guidelines, including those with: (a) Uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus, ***or*** (b) Aortic stenosis, pulmonic stenosis, or coarctation of the aorta alone**;** 2. For the CLD/CHD cohort: (a) Subjects with CLD - infants in their first year of life and a diagnosis of CLD of prematurity requiring medical intervention/management (ie, supplemental oxygen, bronchodilators, or diuretics) within the 6 mths prior to randomisation (b) Subjects with CHD - infants in their first year of life and documented, haemodynamically significant CHD (must be unoperated or partially corrected CHD)**.** ***Note***: Infants with haemodynamically significant acyanotic cardiac lesions must have pulmonary hypertension (≥40 mmHg measured pressure in the pulmonary artery) or the need for daily medication to manage CHD; 3. Infants who are entering their first RSV season at the time of screening**;** 4 Written informed consent obtained from the subject's parent(s)/LAR prior to performing any protocol-related procedures, including screening evaluations; 5. Subject's parent(s)/LAR able to understand and comply with the requirements of the protocol including follow-up and illness visits as judged by the investigator; 6. Subject is available to complete the follow-up period, which will be 1 year after Season 1/ Dose 1 for subjects without CLD/CHD, or 1 yr after Season 2/Dose 1 (or last replacement dose as applicable for CHD) for subjects with CLD/CHD **Exclusion Criteria:** 1. Any fever (≥100.4°F [≥38.0°C], regardless of route) or acute illness within 7 days prior to randomisation; 2. Any history of LRTI or active LRTI prior to, or at the time of, randomisation; 3. Known history of RSV infection or active RSV infection prior to, or at the time of, randomisation; 4. Hospitalisation at the time of randomisation, unless discharge is expected within the 7 days after randomisation; 5. Requirement for mechanical respiratory or cardiac support at the time of randomisation; 6

Anticipated cardiac surgery within 2 wks after randomisation; 7. Anticipated survival of <6 mths after randomisation; 8. Receipt of any investigational drug; 9. Known renal impairment; 10. Known hepatic dysfunction including known or suspected active or chronic hepatitis infection; 11. Clinically significant congenital anomaly of the respiratory tract; 12. Chronic seizure, or evolving or unstable neurologic disorder; 13. Prior history of a suspected or actual acute life-threatening event; 14. Known immunodeficiency, including HIV; 15. Mother with HIV (unless child proven to be uninfected); 16. Any known allergy, including to immunoglobulin products, or history of allergic reaction; 17. Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination; 18. Receipt of any monoclonal or polyclonal antibody or anticipated use during the study; 19. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of subject safety or study results; 20. Concurrent enrollment in another interventional study; 21. Children of employees of the sponsor, clinical study site, or any other individuals; involved with the study conduct, or immediate family members of such individuals.

7.2.2.2. Study treatments

Figure 4. Dosing Regimen: Season 1 – Preterm Cohort and CLD/CHD Cohort in MEDLEY

MEDI8897 Group

Visit	Visit 2/Day 1 [a]	Visit 3/Day 15	Visit 4/Day 31	Visit 5/Day 61	Visit 6/Day 91	Visit 7/Day 121
Dose	1	*No treatment*	2	3	4	5
	MEDI8897 [b] 50 mg if < 5 kg or 100 mg if ≥ 5 kg IM	----	Placebo IM	Placebo IM	Placebo IM	Placebo IM

Palivizumab Group

Visit	Visit 2/Day 1 [a]	Visit 3/Day 15	Visit 4/Day 31	Visit 5/Day 61	Visit 6/Day 91	Visit 7/Day 121
Dose	1	*No treatment*	2	3	4	5
	Palivizumab [b] 15 mg/kg IM	----	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM

Figure 5. Dosing Regimen: Season 2 – CLD/CHD Cohort, MEDI8897 Gp in Season 1 in MEDLEY

MEDI8897 Group

Visit	Visit 10/Day 1	Visit 11/Day 15	Visit 12/Day 31	Visit 13/Day 61	Visit 14/Day 91	Visit 15/Day 121
Dose	1	*No treatment*	2	3	4	5
	MEDI8897 200 mg IM	----	Placebo IM	Placebo IM	Placebo IM	Placebo IM

Figure 6. Dosing Regimen: Season 2 – CLD/CHD Cohort, Palivizumab Gp in Season 1 in MEDLEY

MEDI8897 Group

Visit	Visit 10/Day 1	Visit 11/Day 15	Visit 12/Day 31	Visit 13/Day 61	Visit 14/Day 91	Visit 15/Day 121
Dose	1	*No treatment*	2	3	4	5
	MEDI8897 200 mg IM	----	Placebo IM	Placebo IM	Placebo IM	Placebo IM

Palivizumab Group

Visit	Visit 10/Day 1	Visit 11/Day 15	Visit 12/Day 31	Visit 13/Day 61	Visit 14/Day 91	Visit 15/Day 121
Dose	1	*No treatment*	2	3	4	5
	Palivizumab [a] 15 mg/kg IM	----	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM	Palivizumab 15 mg/kg IM

See Figures 4-6.

Season 1, Preterm and CLD/CHD Cohorts: Subjects randomised 2:1 to MEDI8897 gp (≈600 subjects, including ≈400 subjects in the preterm cohort and ≈200 subjects in the CLD/CHD cohort) or palivizumab gp (≈300 subjects, including ≈200 subjects in the preterm cohort and ≈100 subjects in the CLD/CHD cohort). MEDI8897 gp will receive a single fixed IM dose of MEDI8897 followed by 4 x once-mthly IM placebo. The MEDI8897 dose is stratified by weight band, i.e. 50 mg for infants weighing <5 kg or 100 mg for infants weighing ≥5 kg. Palivizumab gp subjects will receive 5 x once-mthly IM doses of 15 mg/kg palivizumab.

Season 2, CLD/CHD Cohort Only

• Subjects with CLD/CHD ≤24 mths of age who were randomised to the MEDI8897 gp for Season 1 receive a single IM dose of 200 mg followed by 4 x once-mthly IM placebo (≈200 subjects).

• Subjects with CLD/CHD ≤24 mths of age who were randomised to the palivizumab gp for Season 1 will be re-randomised 1:1 to either MEDI8897 or palivizumab. Subjects in the MEDI8897 gp will receive a single IM dose of 200 mg MEDI8897 followed by 4 x once-mthly IM placebo (≈50 subjects). Subjects in the palivizumab gp will receive 5 x once-mthly IM doses of 15 mg/kg palivizumab (≈50 subjects).

7.2.2.3. Efficacy variables and outcomes

See **Table 14.**

7.2.2.4. Randomisation and blinding methods

Randomisation: IWRS used for randomisation to a treatment gp and assignment of blinded IP kit nos. **Blinding:** This is a double-blind study in which MedImmune (Sponsor) provided sites with MEDI8897 and palivizumab. Sites use commercially available saline as the placebo. Syringe barrels covered by the unblinded investigational product manager. Neither the subject/LAR nor the investigator/any site staff involved in the treatment or clinical evaluation of the subjects will be aware of treatment received. Blinding performed at site level to ensure that MEDI8897, placebo, palivizumab are indistinguishable in appearance and are not labelled to reveal treatment identity.

7.2.2.5. Analysis populations

Safety of MEDI8897 summarised by treatment gp based on the As-treated Pop'n (= all subjects who receive any IP analysed according to treatment received) for each season, as well as for the 2 consecutive RSV seasons (i.e. Season 1 and Season 2). For the Season 1 summary, the analysis dataset will include the preterm cohort and CLD/CHD cohort, presented by the treatment received in Season 1; for the Season 2 summary and the 2 consecutive-season summary, the analysis dataset will include the CLD/CHD cohort, presented by the treatment received through the 2 seasons. **Efficacy**: All efficacy summaries based on the ITT Pop'n defined as all randomised subjects analysed according to randomised treatment assignment).

7.2.2.6. Sample size

Safety: 600 subjects exposed to MEDI8897 in Season 1 provides a 95% probability of observing at least 1 AE if the true event rate is 0.5%; if no AEs are observed, this study provides 95% confidence that the true event rate is <0.5%. The sample size is for safety consideration. With respect to efficacy, ≈600 subjects will be exposed to MEDI8897, and 300 subjects exposed to palivizumab in Season 1 to observe numerically similar efficacy for both mAbs. Because of the reduced incidence of RSV disease in this pop'n following the introduction of palivizumab, a superiority or non-inferiority design is not practical. A valid non-inferiority margin cannot be established due to the lack of historical efficacy data for the medically attended RSV LRTI endpoint for palivizumab. Therefore, there is no hypothesis testing for efficacy. Using an assumption of a 6% RSV LRTI rate in palivizumab recipients, ≈18 events will be observed in that gp. The 6% RSV LRTI rate (1.9% RSV hospitalisations and 3.9% outpatient RSV illness) was based on a prior study in preterm infants with and without CLD who received palivizumab. Assuming a 6% rate of RSV LRTI in MEDI8897 recipients, 600 MEDI8897 subjects in Season 1

will provide ≈36 events in that gp. However, because of the largely reduced RSV circulation due to COVID-19 pandemic-related measures, the observed event rates could be much lower.

7.2.2.7. Statistical methods

See also **7.2.2.6** above. There are 3 planned analyses for this study: primary analysis, Season 2, and the final analysis. The primary analysis will be conducted after all randomised subjects have completed follow-up through the first 5-mth RSV season (i.e. Season 1 Day 151 visit) and include all available Season 1 safety, efficacy, PK, and ADA data at the time of data cutoff. The Season 2 analysis will be conducted after all CLD/CHD subjects have completed follow-up through the second 5-mth RSV season (i.e. Season 2 Day 151 visit) and include all available Season 1 data and Season 2 safety, efficacy, PK, and ADA data at the time of data cutoff. The final analysis will be conducted when all subjects have completed the last visit of the study and include all data collected in the study.
Safety: Safety of MEDI8897 will be summarised by treatment gp based on the As-treated Pop'n (=all subjects who receive any IP analysed according to treatment received) for each season, as well as for the 2 consecutive RSV seasons. For Season 1 summary, the analysis dataset will include subjects from the preterm cohort and CLD/CHD cohort, presented by the treatment received in Season 1; for Season 2 summary and the 2 consecutive-season summary, the analysis dataset will include subjects from the CLD/CHD cohort, presented by treatment received through the 2 seasons. All safety variables summarised descriptively between the nirsevimab and the palivizumab gps in Season 1 (through 360 days post first dose in Season 1) and between the cross-over gps in Season 2 (through at least 150 days post first dose in Season 2). AEs will be graded according to the NCI CTCAE where applicable for paediatric assessments. AEs coded by MedDRA and the type, incidence, severity, and relationship to study drug will be summarised by treatment gp. AESIs (as per **Study 3 and 4**), and NOCDs.
Efficacy: Based on the ITT Pop'n. Incidence of MA RSV LRTI through 150 days post Dose 1 in Season 1, based on RSV test results and objective protocol defined LRTI criteria, is the primary efficacy endpoint and will summarised by Season 1 treatment gp for all 900 subjects. The 95% CI of the percentage of subjects meeting the primary efficacy endpoint will be presented by treatment gp. In addition, incidence of RSV LRTI through 150 days post Dose 1 in Season 2 will be summarised for the 300 subjects in the CLD/CHD cohort based on the treatment assignments through Season 1 and Season 2. The incidence of RSV hospitalisation through 150 days after dosing will be summarised by treatment gp using a similar strategy as described for RSV LRTI.
PK: Individual MEDI8897 and palivizumab serum conc'n data tabulated by treatment gp along with descriptive statistics. PK parameters estimated using non-compartmental analysis, if data permit. **ADA**: ADA to MEDI8897 and palivizumab will be assessed and summarised by nos. and percentage of ADA positives by treatment gp. The impact on PK, and safety will be assessed.
RSV nAb: Individual MEDI8897 and palivizumab serum anti-RSV nAb levelstabulated by treatment gp along with descriptive statistics. Anti-RSV nAb levels in serum summarised by GMT and GMFR and corresponding 95% CI for each treatment gp at each visit. Anti-RSV nAb level $t_{1/2}$ will be estimated using non-compartmental analysis, if data permit.
RSV serology: Analysis of anti-RSV antigens antibody levels in serum in MEDI8897 and palivizumab recipients summarised by GMT and GMFR and corresponding 95% CI for each treatment gp at each visit. Seroresponses in MEDI8897 and palivizumab recipients will be determined by examining the fold-rise in antibodies to Ga, Gb, and N antigens.
Healthcare Resource Utilisation (HRU) and caregiver burden: HRU and caregiver burden summaries will be performed on the ITT Pop'n. Caregiver burden for subjects with MA LRTI (protocol defined) caused by RT-PCR-confirmed RSV will be summarised by treatment gp.
RSV resistance: Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + hMPV real-time RT-PCR assay (Quidel Corp). RSV genotypic analysis will report the sequence changes in the mature F protein from all RSV isolates compared to contemporary RSV A and RSV B reference strains. Susceptibility to both mAbs of novel RSV variants will be compared to control viruses.

RSV LRTI occurring from Day 152 to Day 361: The incidence of MA RSV LRTI from Day 152 to Day 361 for Season 1 and Season 2 will be based on RSV test results (performed centrally via RT-PCR) and objective clinical LRTI criteria and summarised by treatment gp.

7.2.2.8. Participant flow

The Primary Analysis was conducted after all randomised subjects had completed follow-up through the first 5-mth RSV season (=Season 1 Day 151 visit). This analysis included all available Season 1 safety, efficacy, PK, and ADA data at the time of the Data Cut-off (DCO) (03-May-2021) through at least 150 days post first dose. The Season 2 Analysis was conducted after all subjects in the CLD/CHD cohort who participated in the Season 2 phase of the study had completed follow-up through a second 5-mth RSV season (=Season 2 Day 151 visit). This analysis included all available Season 2 safety, efficacy, PK, and ADA data at the time of the DCO (30-Apr-2022) through at least 150 days post first dose. The Season 2 Analysis also included all available Season 1 data up to the Season 1 Day 361 visit (i.e. through 360 days post first dose [the end of Season 1]).

In Season 1 (**Table 16**), 925 subjects were randomised (616 nirsevimab, 309 palivizumab), including 615 subjects in the preterm cohort (612/615 were dosed) and 310 subjects in the CLD/CHD cohort (306/310 dosed). For the key subpop'ns representing the unique pop'ns in this study, 200 infants born <29 wGA, 104 infants with CHD, and 217 infants with CLD were randomised. Overall, the majority of subjects completed the efficacy follow-up through at least 150 days post first dose (96.3% nirsevimab [593/616 subjects], 94.8% palivizumab [293/309 subjects]) and (88.1% nirsevimab [543/616 subjects], 85.1% palivizumab [263/309 subjects]) completed the efficacy follow-up through 360 days post first dose (i.e. completed Season 1).

In Season 2 (**Table 17**), 262 subjects from the Season 1 CLD/CHD cohort proceeded into the Season 2 phase of the study. Those subjects from the CLD/CHD cohort who had received nirsevimab in Season 1 received a second dose of nirsevimab in Season 2 (n = 180; = the NIRS/NIRS gp). Those subjects from the CLD/CHD cohort who received palivizumab in Season 1 were randomised 1:1 to a second course of palivizumab (n = 42; =the PALI/PALI gp) or to nirsevimab (n = 40; the PALI/NIRS gp) in Season 2. Overall, the majority of subjects completed the efficacy follow-up through at least 150 days post first dose (96.7% [174/180 subjects], 95.0% [38/40 subjects], and 95.2% [40/42 subjects]) and (38.3% [69/180 subjects], 45.0% [18/40 subjects], and 40.5% [17/42] subjects) completed follow-up through 360 days post first dose (i.e. completed Season 2) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI gps, respectively.

Table 16. Analysis Pop'ns (Season 1) in MEDLEY

	ITT Population [a]			As-treated Population [b]		
	Palivi-zumab	Nirse-vimab	Total	Palivi-zumab	Nirse-vimab	Total
Overall population	309	616	925	304	614	918
Preterm cohort	208	407	615	206	406	612
CLD/CHD cohort	101	209	310	98	208	306
CHD	34	70	104	33	70	103
CLD	70	147	217	68	146	214
GA < 29 weeks	70	130	200	68	128	196
GA < 29 weeks and without CLD or CHD	28	49	77	28	48	76
GA < 32 weeks and with CLD	54	117	171	52	116	168

[a] The ITT Population (Season 1) included all randomised subjects. Subjects in the ITT Population (Season 1) were analysed according to treatment group assigned by randomisation.

[b] The As-treated Population (Season 1) included subjects who were randomised and received any IP in Season 1. Subjects in the As-treated Population (Season 1) were analysed by the IP actually received in Season 1.

CHD = congenital heart disease; CLD = chronic lung disease; GA = gestational age; IP = investigational product; ITT = intent-to-treat.

Source: Table 14.1.5.1, Table 14.1.6.1.1 and Table 14.3.2.1.1.1.

Table 17. Analysis Pop'ns for the CLD/CHD Cohort (Season 2) in MEDLEY

Analysis population	Number of subjects			
	PALI/PALI	PALI/NIRS	NIRS/NIRS	Total
ITT (Season 2)[a]	42	40	180	262

Analysis population	Number of subjects			
	PALI/PALI	PALI/NIRS	NIRS/NIRS	Total
AT (Season 2)[b]	42	40	180	262

[a] Intent-to-treat (ITT) Population (Season 2) included all CHD/CLD subjects enrolled in Season 2. Subjects in ITT Population (Season 2) were analysed according to their randomised treatment group through the 2 seasons.

[b] As-treated Population (Season 2) included CHD/CLD subjects who were randomised and received any amount of investigational product in Season 2. Subjects in As-treated Population (Season 2) were analysed by the investigational product they actually received through the 2 seasons.

AT = As-treated; CHD = congenital heart disease; CLD = chronic lung disease; ITT = intent-to-treat; NIRS = nirsevimab; PALI = palivizumab.
Source: Table 14.1.5.2

7.2.2.9. Major protocol violations/deviations

Protocol Deviations (Season 1): In the overall pop'n, 166 (17.9%), including 111 (18.0%) in the nirsevimab gp and 55 (17.8%) in the palivizumab gp, had at least one important protocol deviation. The most common (>5% total) were treatment compliance (9.0%), inclusion criteria (6.3%), and due to the COVID-19 pandemic (5.5%). The incidence of important protocol deviations was generally balanced between the 2 treatment gps of the overall pop'n and across the preterm and CLD/CHD cohorts, and not felt to impact interpretation of the study results.
Study Disruptions due to COVID-19 (Season 1): In the overall pop'n, 42.6% of subjects (42.5% nirsevimab gp and 42.7% palivizumab gp) were randomised prior to the start of the COVID-19 pandemic (prior to 11-Mar-2020) and 57.4% (57.5% nirsevimab gp and 57.3% palivizumab gp) were randomised after the start of the pandemic. The impact of the pandemic on visits, dosing, study withdrawal was low, with 6.7% of subjects (6.5% nirsevimab gp and 7.1% palivizumab gp) having at least one missed visit, 4.2% of subjects (3.9% nirsevimab gp and 4.9% palivizumab gp) having at least one missed dose, and 0.5% of subjects (0.3% nirsevimab gp and 1.0% in the palivizumab gp) withdrawing from the study during Season 1. All COVID-19 study disruptions were balanced between the gps and were consistent across the overall pop'n and preterm and CLD/CHD cohorts. The COVID-19 pandemic is not judged to meaningfully impact the overall quality of the study data.
Protocol Deviations for the CLD/CHD Cohort (Season 2): 14 subjects (5.3%), including 13 (7.2%) in the NIRS/NIRS gp, 1 (2.5%) in the PALI/NIRS gp, and 0 in the PALI/PALI gp, had at least one important protocol deviation. The most common (>2% total) deviations were treatment compliance deviations and LRTI sample deviations. Incidence of important protocol deviations was generally balanced between the 3 treatment gps. The important protocol deviations did not impact interpretation of the study results. All subjects were randomised/ assigned to treatment gps in the Season 2 phase of the study after the start of the COVID-19 pandemic. The impact of the pandemic on visits, dosing, and study withdrawal was generally low, with a total of 0.8% of subjects (0.6%, 0%, and 2.4%, in the NIRS/NIRS, PALI/NIRS, and PALI/PALI gps, respectively) having at least one missed visit, no subjects having at least one missed dose, and no subjects withdrawing from the study during Season 2. The COVID-19 pandemic is not judged to meaningfully impact the overall quality of the study data.

7.2.2.10. Baseline data

Generally balanced between treatment gps in the overall pop'n and the preterm and CLD/CHD cohorts. In the overall pop'n, the majority were White (79.2%) not Hispanic or Latino (84.8%), and ≈half were male (53.5%), with a median age at randomisation of 3.5 mths (range, 0.07 to 12.25 mths). More than half of the subjects weighed <5 kg on Day 1 (56.5%) and were preterm infants with a gestational age of <35 wks (85.1%); 21.6% of subjects were <29 wGA, 21.5% of subjects were ≥29 to <32 wGA, and 41.9% of subjects were ≥32 to <35 wGA. Twelve subjects had Down syndrome (1.3%) and 2 subjects had CF (0.2%). In Japan, only 1 subject with Down

syndrome (without CLD or CHD) was included in the CLD/CHD cohort. The demographic and baseline characteristics of the preterm and CLD/CHD cohorts were generally consistent with those of the overall pop'n, with the exception of key baseline characteristics specific to each cohort (i.e. gestational age differences and presence or absence of CLD/CHD and associated disorders such as underlying lung disease). For subjects entering Season 1, median weight on Season 1 Day 1 was 4.5 kg (range, 1.7 to 12.2 kg). For subjects entering Season 2, median weight on Season 2 Day 1 was 9.9 kg (range, 6.1 to 15.7 kg).

7.2.2.11. Results for the primary safety outcome

Season 1 Safety Results (Through 360 Days Post First Dose in Season 1): Through 360 days post first dose in Season 1, nirsevimab had a similar AE profile compared palivizumab, in the overall pop'n and preterm and CLD/CHD cohorts, including infants with CLD, CHD, and those born <29 wGA. Types and frequencies of AEs generally balanced between the nirsevimab and palivizumab gps, with a low incidence of IP-related events (including IP-related skin reactions), investigator assessed AESIs, and NOCDs. There were no IP-related ≥Grade 3 events, IP-related SAEs, or IP-related NOCDs. In the overall pop'n, 444/614 subjects (72.3%) and 215/304 subjects (70.7%) in the nirsevimab and palivizumab gps, respectively, had at least one AE. A majority of the events were Grade 1 or 2 severity. The most common AEs (>10% of subjects) reported for nirsevimab (vs. palivizumab) were URTI; 24.1%[148/614 subjects] vs. 25.7% [78/304 subjects]), pyrexia (13.5% [83/614 subjects] vs. 14.1% [43/304 subjects]), rhinitis (12.2% [75/614 subjects] vs 13.2% [40/304 subjects]), and nasopharyngitis (9.3% [57/614 subjects] vs. 12.8% [39/304 subjects]). The rate of AEs considered by the investigator to be IP-related was low and similar between the nirsevimab and palivizumab gps (1.6% [10/614 subjects] vs. 2.0% [6/304 subjects]). The most common IP-related AEs (≥2 subjects in either gp) reported for nirsevimab (vs. palivizumab) were agitation (3 vs. 0 subjects), body temperature increased (2 vs. 0 subjects), and pyrexia (1 vs. 2 subjects). There were no observed events of anaphylaxis or serious allergic reactions attributed to nirsevimab. Three AESIs were reported by investigators, all in the nirsevimab arm, including 1 AESI of hypersensitivity and 2 AESIs of thrombocytopaenia: (1) rash maculo-papular (assessed as a skin hypersensitivity reaction), which occurred on the same day as a placebo IP dose and 92 days post active dose of nirsevimab; the event was considered IP-related and the subject was withdrawn from IP the same day; (2) heparin-induced thrombocytopaenia 51 days post active dose of nirsevimab and considered unrelated to IP, in an infant with CHD who also received a dose of palivizumab outside the study prior to this event; and (3) thrombocytopaenia, considered unrelated to IP, 39 days post active dose of nirsevimab, reported on the same day as an event of sepsis, in an infant with CHD who also had nosocomial pneumonia and subsequently died. AESI based on selected compatible MedDRA PTs generally similar between the nirsevimab and palivizumab gps in the overall pop'n and preterm cohort. In the CLD/CHD cohort, the incidence of AESIs based on selected MedDRA PTs through 360 days post first dose in the nirsevimab gp was numerically higher compared with the palivizumab gp (23.6% [49/208 subjects] vs. 15.3% [15/98 subjects]), driven by a higher incidence of events compatible with PTs in the hypersensitivity (including anaphylaxis) category. AEs through 30 days post first dose were evaluated as post-hoc analyses to permit an assessment of AEs relative to the active nirsevimab dose since subjects in the nirsevimab gp received an active dose followed by 4 once-mthly placebo doses. The types and frequency of AEs within 30 days post first dose were generally balanced between the nirsevimab and palivizumab gps for the overall pop'n and preterm and CLD/CHD cohorts. Notably, the numerical difference in the incidence of AESIs based on selected MedDRA PTs between the nirsevimab and palivizumab gps in the CLD/CHD cohort was not seen within all analysed time points through 30 days post first dose (i.e. within 1, 3, 7, 14, and 30 days post first dose). Two subjects in each of the nirsevimab (0.3% [2/614]) and palivizumab (0.7% [2/304]) gps had Grade 1 IP-related skin reactions. Skin AEs are discussed in **Section 8**.

Table 18. Overall Summary of TEAEs for Overall Pop'n, Preterm and CLD/CHD Cohorts Through 360 Days Post in MEDLEY First Dose in Season 1 – As-treated Pop'n (Season 1)

Subjects [a] with	Number (%) of subjects					
	Overall		Preterm		CLD/CHD	
	Palivizumab (N = 304)	Nirsevimab (N = 614)	Palivizumab (N = 206)	Nirsevimab (N = 406)	Palivizumab (N = 98)	Nirsevimab (N = 208)
≥1 IP-related event of ≥Grade 3 [b]	0	0	0	0	0	0
Any AE with outcome death	1 (0.3)	5 (0.8)	0	2 (0.5)	1 (1.0)	3 (1.4)
≥1 serious [c] event	38 (12.5)	80 (13.0)	13 (6.3)	35 (8.6)	25 (25.5)	45 (21.6)
≥1 serious [c] and/or ≥Grade 3 [b] event	39 (12.8)	84 (13.7)	13 (6.3)	35 (8.6)	26 (26.5)	49 (23.6)
≥1 IP-related serious [c] event	0	0	0	0	0	0
≥1 AESI based on investigator assessments	0	3 (0.5)	0	1 (0.2)	0	2 (1.0)
≥1 AESI based on selected MedDRA PT codes	47 (15.5)	117 (19.1)	32 (15.5)	68 (16.7)	15 (15.3)	49 (23.6)
≥1 IP-related AESI based on selected MedDRA PT codes	1 (0.3)	2 (0.3)	1 (0.5)	1 (0.2)	0	1 (0.5)
≥1 IP-related skin reaction	2 (0.7)	2 (0.3)	1 (0.5)	1 (0.2)	1 (1.0)	1 (0.5)
≥1 NOCD	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)
≥1 IP-related NOCD	0	0	0	0	0	0
≥1 event related to COVID-19	6 (2.0)	17 (2.8)	2 (1.0)	11 (2.7)	4 (4.1)	6 (2.9)
≥1 confirmed COVID-19 [d]	6 (2.0)	15 (2.4)	2 (1.0)	10 (2.5)	4 (4.1)	5 (2.4)
≥1 suspected COVID-19	0	2 (0.3)	0	1 (0.2)	0	1 (0.5)

[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).

TE NOCDs reported in 2 subjects in the nirsevimab gp: nonserious Grade 2 asthma in the preterm cohort on Day 192, and serious Grade 2 calculus urinary in the CLD/CHD cohort on Day 101. Neither of the events were considered to be IP-related. Five fatal events occurred in the nirsevimab arm in Season 1: 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 arm: bronchiolitis in an infant in the CLD/CHD cohort. All fatal events were judged as unrelated to IP. In the overall pop'n, frequency of SAEs similar between nirsevimab and palivizumab gps (13.0% [80/614 subjects] vs. 12.5% [38/304 subjects]). The most common SAEs (>2 subjects) for nirsevimab subjects (vs. palivizumab subjects) were bronchiolitis (12 vs. 4), gastroenteritis (6 vs. 1), bronchitis (5 vs. 2), pneumonia (5 vs. 1), RSV bronchiolitis (4 vs. 2), COVID-19 and viral URTI (3 vs. 1 each). None of the SAEs considered IP-related.

Summary of Season 2 Safety Results (Through at Least 150 Days Post First Dose in Season 2): The AE profile was similar across the treatment gps (NIRS/NIRS, PALI/NIRS, and PALI/PALI), with the types and frequencies of AEs being generally balanced **(Table 19).** Note that the nos. of subjects in the As-treated Pop'n in the PALI/NIRS (n=40) and PALI/PALI (n=42) gps was lower than in the NIRS/NIRS gp (n=180). Incident AESIs low and balanced between treatment gps in the CLD/CHD Cohort in Season 2. ≥Grade 3 events and SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS gps than the PALI/PALI gp; however, this was not observed within all analysed time points through 30 days post first dose. No IP-related AEs, NOCD, or skin hypersensitivity or AESIs in any treatment gp. No deaths in Season 2.

Table 19. Overall Summary of TEAEs Through at Least 150 Days Post First Dose in Season 2 in MEDLEY – As-treated Pop'n (Season 2)

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] 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 selected MedDRA PT codes	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; Grade 5: fatal.

Subjects [a] with	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)

[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 was 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.

In the CLD/CHD Cohort, 126/180 subjects (70.0%), 29/40 subjects (72.5%) and 29/42 subjects (69.0%) in the NIRS/NIRS, PALI/NIRS and PALI/PALI gps, respectively, had at least one AE. The majority were of Grade 1 or Grade 2 severity. The most common AEs (>10%) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI gps were URTI (25.0% [45/180 subjects], 17.5% [7/40 subjects], and 16.7% [7/42 subjects]), nasopharyngitis (12.2% [22/180 subjects], 15.0% [6/40 subjects], and 21.4% [9/42 subjects]), pyrexia (11.7% [21/180 subjects], 20.0% [8/40 subjects], and 11.9% [5/42 subjects]), rhinitis (12.2% [22/180 subjects], 10.0% [4/40 subjects], and 14.3% [6/42 subjects]), diarrhoea (5.0% [9/180 subjects], 5.0% [2/40 subjects], and 11.9% [5/42 subjects]), respectively.

No observed events of anaphylaxis or serious allergic reactions. No AESIs based on investigator assessment reported in Season 2. AESI based on selected MedDRA PTs comparable between treatment gps in the CLD/CHD Cohort (13.3% [24/180], 10.0% [4/40 subjects], and 9.5% [4/42], in the NIRS/NIRS, PALI/NIRS, and PALI/PALI gps, respectively). In the CLD and CHD subpop'ns, the only notable difference between the treatment gps was that in the CHD subp'n AESIs based on selected MedDRA PTs occurred at a numerically higher rate in the NIRS/NIRS (23.2% [13/56]) and PALI/NIRS (21.4% [3/14]) treatment gps compared with PALI/PALI

(9.1% [1/11]). However, this imbalance was not observed within all analysed time points through 30 days post first dose in Season 2. For TEAEs within 30 days post first dose in Season 2 by SOC and PT, no clinically meaningful imbalances in favour of any treatment gp in the CLD/CHD cohort. Incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS gps than the PALI/PALI gp (9.4% [17/180] vs. 10.0% [4/40] vs. 0% [0/42], respectively). The most common SAEs (≥2 subjects) in the NIRS/NIRS, PALI/NIRS and PALI/PALI gps were bronchitis viral (3 vs. 0 vs. 0), COVID-19 (2 vs. 0 vs. 0), gastroenteritis (2 vs. 0 vs. 0), LRTI (2 vs. 1 vs. 0), and URTI (2 vs. 0 vs. 0), respectively.

7.2.2.1. Results for other efficacy outcomes

Descriptive Efficacy: Incidence of MA RSV LRTI through 150 days post first dose in Season 1 was low and balanced: 0.6% (4/616 subjects) nirsevimab gp vs. 1.0% (3/309 subjects) palivizumab gp. Overall disease incidence in each of the nirsevimab and palivizumab gps was distributed between the preterm cohort (0.5% [2/407 subjects] vs. 0.5% [1/208 subjects]) and CLD/CHD cohort (1.0% [2/209 subjects] vs 2.0% [2/101 subjects]). The incidence of MA RSV LRTI with hospitalisation through 150 days post first dose in Season 1 was 0.3% (2/616) nirsevimab gp vs. 0.6% (2/309) palivizumab gp. All of these events occurred in the CLD/CHD cohort (1.0% nirsevimab [2/209], 2.0% palivizumab [2/101]). For both MA RSV LRTI and MA RSV LRTI with hospitalisation, while nos. of events were small, all events in the nirsevimab arm were RSV A. Incidence of All MA LRTI (any cause) in Season 1 was balanced across treatment gps in the overall pop'n and in the preterm and CLD/CHD cohorts. In the overall pop'n, there was no MA RSV LRTI or MA RSV LRTI with hospitalisation through 150 days post first dose in Season 2 in any treatment gp. Season 2 MA LRTI (any cause) was low in all 3 treatment gps.
PK results (Season 1 and 2): In both Season 1 and 2, nirsevimab conc'ns declined linearly over time. In Season 1, there was substantial overlap in serum conc'ns between weight gps (<5 kg, ≥5 kg), with comparable serum conc'ns in preterm and CLD/CHD subjects. In CLD/CHD subjects, serum conc'ns were slightly higher in Season 2, with substantial overlap in the serum conc'ns observed for the weight-band dose in Season 1 and the fixed dose in Season 2.
Immunogenicity Results (Season 1 and 2): In Season 1 phase, 86.8% (797/918) of the overall study pop'n who received study treatment had samples available for ADA assessment at Day 361. Of the 262 subjects in the CLD/CHD cohort who participated in the Season 2 phase of the study and received either a first or second dose (nirsevimab) or course (palivizumab), 88.2% (231/262) of subjects had ADA samples available at Season 2 Day 151 (158/180 [87.8%] in the NIRS/NIRS gp, 37/40 [92.5%] in the PALI/NIRS gp, and 36/42 [85.7%] in the PALI/PALI gp), and 37.0% (97/262) of subjects had ADA samples at Season 2 Day 361 (66/180 [36.7%] in the NIRS/NIRS gp, 17/40 [42.5%] in the PALI/NIRS gp, and 14/42 [33.3%] in the PALI/PALI gp). The subjects from the preterm cohort did not participate in the Season 2 phase of the study.
Of the subjects with samples available for testing during Season 1, ADA was detected at any time post-baseline through Day 361 in 5.8% (34/587) of subjects in the nirsevimab gp overall, including 6.2% (24/385) of subjects in the preterm cohort and 5.0% (10/202) in the CLD/CHD cohort. At Season 1 Day 361, 6.0% (32/534) of subjects in the nirsevimab gp overall, including 6.6% (23/348) in the preterm cohort and 4.8% (9/186) in the CLD/CHD cohort, were ADA positive. Although the proportion of subjects with ADA to nirsevimab in Season 1 was small, a comparison of the safety profiles of those who were ADA positive vs. ADA negative, revealed no apparent impact on safety of nirsevimab through 360 days post first dose of Season 1. For the 180 CLD/CHD subjects in the NIRS/NIRS gp in Season 2 with available samples, ADA detected in 7/173 (4.0%) subjects at Day 361 of Season 1. At Day 31 and Day 151 of Season 2, ADA detected in 1/90 (1.1%) and 0/158 (0.0%) subjects, respectively, showing that there was no immune priming by receipt of prior nirsevimab. All subjects with any post baseline ADA in Season 1 had no detectable ADA in Season 2, showing that the second nirsevimab dose (Season 2 Day 1) did not boost the immune response. ADA in either Season 1 or Season 2 in this gp did not appear to impact safety through at least 150 days post first dose in Season 2. No hypersensitivity or other AESI reported in Season 2 for this gp or any treatment gp.

7.2.2.2. Evaluator commentary

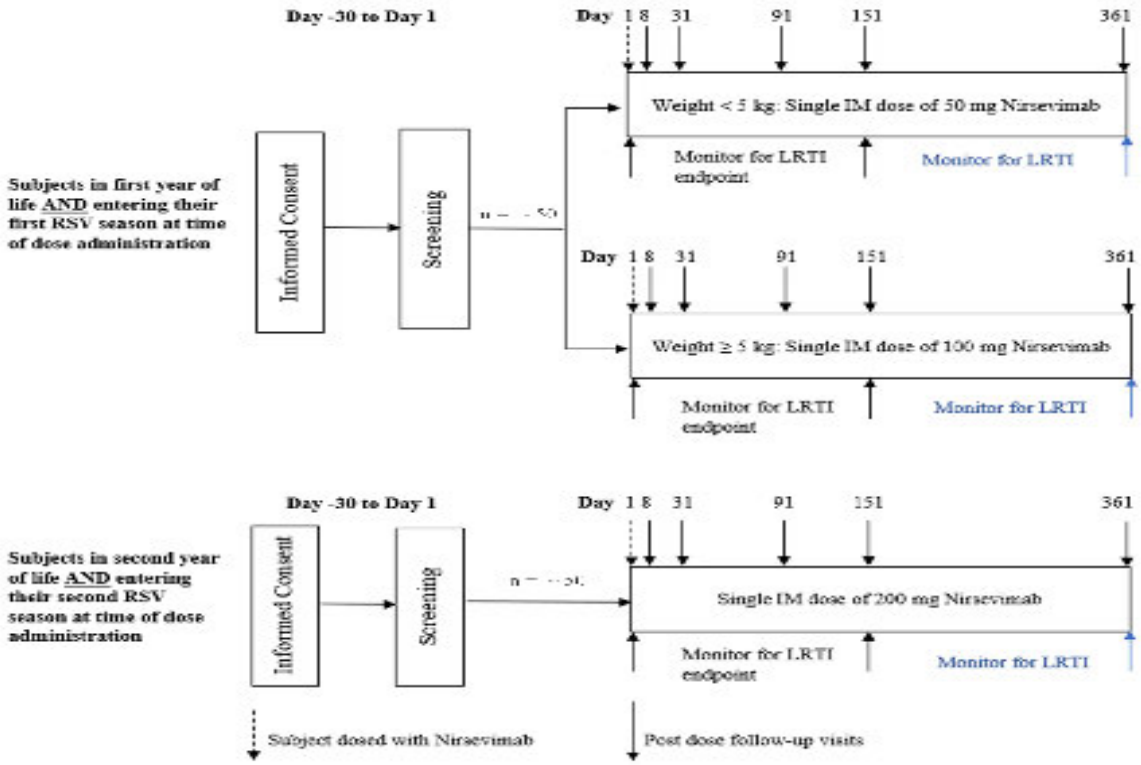
The **MEDLEY** study using weight-based dosing of single dose 50mg or 100mg demonstrates that nirsevimab had comparable safety and tolerability profile to palivizumab, in the overall pop'n, preterm infants, and those with CLD and/or CHD in Season 1, and with comparable safety findings for subjects with CLD/CHD who received nirsevimab (single IM dose of 200mg) in Season 2. Nirsevimab serum conc'ns were comparable in preterm and CLD/CHD subjects in Season 1. Overall, nirsevimab serum conc'ns in CLD/CHD subjects were slightly higher in Season 2 than in Season 1. There is no evidence of immune priming in subjects who had received prior nirsevimab, and no evidence that the second dose of nirsevimab boosted ADA responses in those few subjects who were ADA positive to nirsevimab in Season 1. In both seasons, based on limited data, there was no apparent impact of ADA against nirsevimab on PK and efficacy. In Season 1, incidence of both MA RSV LRTI and MA RSV LRTI with hospitalisation were low and balanced between treatment gps in the overall pop'n and across the preterm and CLD/CHD cohorts. In Season 2, there were no incidences of either MA RSV LRTI or MA RSV LRTI with hospitalisation through 150 days post the Season 2 Day 1 dose – possibly reflecting the impact of public health measures against COVID-19 impacting on lower rates of circulating RSV. There was no indication of increased or worsening AEs in subjects who received nirsevimab in the 2 consecutive seasons (including no indication of increased hypersensitivity), or in those subjects who received nirsevimab in Season 2, subsequent to receiving palivizumab in Season 1.

7.3. Other efficacy studies

7.3.1. Study ID- D5290C00008 (Study 6, 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

Design: Phase 2, open-label, uncontrolled, single-dose study to evaluate safety and tolerability, PK, occurrence of ADA, and efficacy of nirsevimab in immunocompromised (IC) children who are ≤24 mths of age at the time of dose administration.
Sites: 22 sites in 6 countries; the study is ongoing and is planned to be conducted at up to 35 sites in 8 countries.
Dates: First subject enrolled: 19-Aug-2020; ongoing. The analyses presented in this report are based on a data cut-off date of 16-May-2022 and a clinical data lock date of 27-Jun-2022.
Key protocol amendment: Protocol Amendment 3 (dated 23 June 2021 for global amendment, 4 July 2021 for Japan amendment): The principal reason for this amendment is to revise the protocol to be globally applicable, in line with the decision to expand the study to include countries other than Japan. By expanding the study to additional countries and increasing sample size, IC children with different underlying causes from different countries can be included, supporting the safety evaluation in a diverse pop'n.
Methods: See Figure 7.
Statistical Methods: Sample size expanded to 100 planned to receive a single IM dose of nirsevimab to evaluate the safety, PK, ADA, and efficacy, and assessed descriptively. To evaluate risk, a sample size of 100 subjects exposed to nirsevimab in this Phase II study would provide a 95% probability of observing at least 1 AE if the true event rate is 3%; if no AEs were observed, this study provides 95% confidence that the true event rate is ≤3%.
Safety Analyses: AEs graded according to current vn. Of NCI CTCAE where applicable for paediatric assessments, and coded according to MedDRA and the type, incidence, severity, and relationship to IP will be summarised. AESI and NOCDs recorded as per the other studies.
PK Analyses: Serum conc'ns of nirsevimab at selected time points evaluated to confirm that adequate exposures for protection from RSV LRTI are maintained for at least 5 mths after dosing. Nirsevimab serum conc'n data will be presented in descriptive statistics. PK parameters estimated using noncompartmental analysis, if data permit. **ADA Analyses:** The incidence of

ADA to nirsevimab assessed and summarised by nos. and percentage of subjects who are ADA positive. Impact of ADA on PK, and associations with TEAEs and TESAEs will be assessed.
Efficacy Analyses: Incidence of MA RSV LRTI through 150 days post dose, based on RSV test results (central RT-PCR testing) and objective protocol-defined LRTI criteria, will be summarised for all dosed subjects. For subjects with multiple MA RSV LRTI events, only the first occurrence will be used in the analysis.
Additional Analyses. RSV nAb: Serum anti-RSV NAb levels in nirsevimab recipients will be summarised by GMC and GMFR and corresponding 95% CI at each visit; **RSV Serology:** Analysis of serum antibody levels to RSV antigens in nirsevimab recipients will be summarised by GMC and GMFR and corresponding 95% CI at each visit. Seroresponses in nirsevimab recipients will be determined by examining the fold-rise in antibodies to RSV F, Ga, Gb, and N antigens.
RSV Resistance to Nirsevimab: Genotypic analysis of the full-length mature F protein will be conducted on all RSV-positive isolates confirmed centrally using the Lyra RSV + hMPV real-time RT-PCR assay manufactured (Quidel Corp).
Figure 7. Study Flow Diagram in MUSIC



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

Duration of treatment: Subjects entering their first RSV season will receive a single fixed IM dose of nirsevimab 50 mg if body weight <5 kg or 100 mg if body weight ≥5 kg (n = ~15), and subjects entering their second RSV season will receive a single fixed IM dose of nirsevimab 200 mg (n = ~15). Batch A0390A.
Key inclusions: Neonate, infant, or young child ≤24 mths of age who, per Investigator judgment, are: (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
2. The subject must meet at least 1 of the following conditions at the time of informed consent (a) Diagnosed with combined immunodeficiency or other immunodeficiency (Wiskott-Aldrich syndrome, DiGeorge syndrome, etc), or (b) Diagnosed with HIV, or (c) History of organ or bone marrow transplantation, or (d) Subject is receiving immunosuppressive chemotherapy, or (e) Subject is receiving systemic high-dose corticosteroid therapy, or (f) receiving other immunosuppressive therapy (e.g. azathioprine, methotrexate, etc); 3. Written informed consent from the subject's parent(s)/LAR(s) prior to performing any protocol-related procedures, including screening.

Primary and Secondary endpoint: See Table 20. Primarily, the PK data will be used to assess whether nirsevimab systemic exposure is altered in this IC pop'n vs. healthy infants.

Table 20. OBJECTIVES AND ASSOCIATED ENDPOINTS in MUSIC

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age.	All TEAEs, TESAEs, AESIs, and NOCDs.
Secondary	
To evaluate the PK of nirsevimab.	Summary of nirsevimab serum concentrations.
To evaluate the ADA responses to nirsevimab in serum.	Incidence of ADA to nirsevimab in serum.
To assess the efficacy of nirsevimab when administered as a single IM dose to infants ≤ 24 months of age.	Incidence of medically attended LRTI (inpatient and outpatient) and hospitalisations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab.
Exploratory*	
To determine anti-RSV neutralising antibody levels in serum afforded by a single dose of nirsevimab.	Anti-RSV neutralising antibody levels in serum for nirsevimab.
To evaluate exposure to RSV by measuring seroresponses to different RSV proteins.	Antibody levels to RSV F, Ga, Gb, or N at different time points. Changes in antibody levels (seroresponse) indicating exposure to RSV.
To characterise resistance to nirsevimab through genotypic and phenotypic analyses.	Genotypic analysis and susceptibility of RSV variants to neutralisation by nirsevimab.

Objectives	Endpoints
To assess HRU for nirsevimab recipients.	Magnitude of HRU (eg, number of admissions to hospitals and ICUs, and duration of stay; number of subjects who require respiratory support and supplemental oxygen and duration of use; number and type of outpatient visits, eg, ER, urgent care, outpatient clinic; and number of prescription and OTC medications) for nirsevimab recipients.

* The exploratory objectives and endpoints were not analysed as part of the interim analysis. The genotypic and phenotypic analyses will be reported separately from this CSR.

ADA = antidrug antibody; AESI = adverse event of special interest; ER = emergency room; HRU = healthcare resource utilisation; ICU = intensive care unit; IM = intramuscular; LRTI = lower respiratory tract infection; NOCD = new onset of chronic disease; OTC = over the counter; PK = pharmacokinetics; RSV = respiratory syncytial virus; RT-PCR = reverse transcriptase-polymerase chain reaction; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

Results: At the time of the data lock, 151 had been enrolled. At the time of the Interim analysis, 60 subjects had been enrolled through the end of 2021 and dosed; 36 subjects received 50 mg or 100 mg nirsevimab and 24 subjects had received 200 mg nirsevimab.

Demographics and Baseline Disease Characteristics: Majority were male (42 subjects [70.0%]), either Asian (28 subjects [46.7%]) or White (24 subjects [40.0%]), not Hispanic or Latino (53 subjects [88.3%]). Mean birth weight was 3.12 kg, with 8 subjects (13.3%) ≤2.5 kg and 52 subjects (86.7%) >2.5kg; mean gestational age of 38.47 wks. Mean age of subjects at IP administration who received 50 mg/100 mg nirsevimab and who received 200 mg nirsevimab were 7.33 mths and 17.58 mths, respectively. Mean weight of subjects on Day 1 who received 50 mg/100 mg nirsevimab and who received 200mg were 7.04 kg and 10.03 kg, respectively.

Interim Efficacy Results: None of the MA LRTI met the criteria of a protocol defined MA RSV LRTI. One subject (1.7%) experienced an MA RSV LRTI through 150 days post dose (after database lock, site confirmed event was an URTI.

Interim Safety: In total, 48 subjects (80.0%) experienced at least 1 TEAE; the most commonly reported TEAEs were in the SOCs of Infections and infestations, Skin and subcutaneous tissue disorders, and Gastrointestinal disorders. The most commonly reported TEAE by PT was URTI

(21 subjects [35.0%]). The majority of TEAEs were Grade 1 or 2 severity; Grade 3 TEAEs were reported in 16 subjects (26.7%); incidence of Grade 4 and Grade 5 TEAEs were low (2 subjects [3.3%] and 1 subject [1.7%], respectively). One subject (1.7%) experienced a TEAE with the outcome of death (tumour haemorrhage); not considered related to the IP. No NOCD. Eighteen subjects (30.0%) experience TESAEs. and 16 subjects (26.7%) experienced TESAEs of Grade ≥3 severity; no TESAEs considered related to the IP, and all TESAEs were experienced by ≤2 subjects (3.3%) each. IP-related TEAEs were experienced by 5 subjects (8.3%), all of which were of Grade 1 or 2 severity, and all occurred within 7 days of dosing. There were no IP-related TEAEs of anaphylaxis, severe hypersensitivity, or thrombocytopaenia. Four subjects (6.7%) experienced AESIs based on Investigator assessment; all of which were assessed as skin hypersensitivity reactions. No AESI based on Investigator assessment occurred within 1 day of dosing. One subject (1.7%) experienced an IP-related AESI (erythema) within 3 days of dosing. All AESIs based on Investigator assessment were of Grade 1 severity. Fifteen subjects (25.0%) experienced AESIs based on compatible MedDRA PT codes, the majority of which were events compatible with PTs in the hypersensitivity category. One subject (1.7%) experienced an IP-related AESI of hypersensitivity based on MedDRA PT (rash). The majority of AESIs based on compatible MedDRA PT codes were of Grade 1 severity. No subject who developed treatment-emergent ADAs experienced a skin hypersensitivity reaction, an IP-related TEAE, or an AESI. There was no apparent impact on the safety results by the presence of ADAs.
PK: Mean nirsevimab serum conc'ns were larger in those subjects who received 200 mg nirsevimab than those who received 50 mg or 100 mg nirsevimab, with substantial overlap between the two gps. **ADA:** Two subjects (3.3%) developed TE ADAs during the study; both subjects were positive for YTE (M257Y/259T/T261E triple amino acid substitution) and negative for nAbs.

7.3.2. Evaluator commentary: other efficacy studies (MUSIC)

This single-arm study has undergone protocol amendments to increase sample size and has not completed yet. In this highly vulnerable (to RSV) cohort of immunocompromised infants there were no new safety concerns raised in the interim analyses. The weight basing dosing in RSV season 1 was well tolerated, as was the 200mg dose in Season 2, with the caveat that numbers are quite small. There were no protocol-defined MA RSV LRTIs reported, which may be a reflection of the impact on public measures to curtail COVID-19 reducing RSV transmission. Nirsevimab serum conc'ns were as expected based on previous studies in children without immunocompromised conditions. ADA positivity was low 3.3% with no apparent impact on the safety or PK results.

7.4. Analyses performed across trials: pooled and meta analyses

Exposure-Response Analysis supporting extrapolation; Pooled Study MELODY (Primary Cohort) and Study 3 (all subjects). An exposure-response analysis was performed based on pooled data from **MELODY (Primary Cohort) and Study 3 (all subjects).** The primary aim of this analysis was to support extrapolation, as agreed with the EU in the paediatric investigation plan (PIP)**.** $AUC_{baseline}$ CL, derived based individual predictions of CL at baseline (i.e. based on the infant's body weight and postmenstrual age at dosing), was used as the exposure metric. The AUCs were divided into bins based on quartiles of Study 3 data (**see Addendum to 2021 Population PK report, Module 5.3.3.5**). **Study 4** applied weight-band dosing to achieve exposures above the serum Q1 efficacy target and the individual AUCs for **Study 4** subjects were therefore mapped into the bins defined by the quartiles based on **Study 3**. A Cox proportional hazards model, stratified by study and age, was used to evaluate the influence of nirsevimab exposure (AUC quartiles, defined based on **Study 3**) on the time to first MA RSV LRTI through Day 151. The results of the analysis showed that exposures above the first quartile (Q2 to Q4) were significantly different from placebo ($p < 0.001$), with HR point estimates <0.3 The HR for

the first quartile (Q1) was 0.48 (p = 0.024), indicating lower efficacy in this exposure range, confirming exposures >Q1 as the target for efficacy.

Exposure-Based Extrapolation of Efficacy to MEDLEY and MUSIC

MEDLEY evaluated the safety and PK of nirsevimab in a higher-risk (palivizumab-eligible) pop'n following a single fixed weight-band IM dose of nirsevimab (50 mg if <5 kg, 100 mg if ≥5 kg) in Season 1, and 200 mg in Season 2 (See above). No formal hypothesis testing for efficacy was intended in this study. The efficacy of nirsevimab in this pop'n was assessed by PK extrapolation, as agreed with the FDA (End-of-Phase II meeting, Feb 2019). **MUSIC** evaluated safety and PK in IC children entering their first or second RSV season (See above). A similar PK extrapolation approach was taken.

Extrapolation plan The extrapolation of efficacy to higher risk pop'ns entering their first RSV season and vulnerable to severe RSV disease entering their second season relies on the following assumptions:

- Comparable viral aetiology between the paediatric pop'ns healthy preterm and term infants, and the higher-risk pop'ns in **MEDLEY** and **MUSIC**;
- No expected difference in the mechanism of action based on subgp (age or medical condition) since nirsevimab does not bind any endogenous targets in animals or humans;
- Similar expected exposure-response relationship between nirsevimab serum conc'n and RSV neutralising ability across all subgps. Similar expected safety across subgps since nirsevimab does not bind host targets.

Extrapolation was performed applying 2 approaches: 1) comparison of observed nirsevimab serum conc'ns at Day 151 in **MEDLEY** (and **MUSIC**) to those in **MELODY**; 2) comparison of derived exposures in **MEDLEY** (and **MUSIC**) to the efficacy exposure target (per agreed PIP in the EU). The first approach is not model-dependent and therefore relies on fewer assumptions. The second approach included exposure-response analysis of **Study 3** and **MEDLEY** data to define the nirsevimab exposure target, and derivation of individual nirsevimab exposures in **MEDLEY** (and **MUSIC**) from the final popPK model. Efficacy was considered demonstrated if proposed doses resulted in serum nirsevimab exposures at or above the predicted efficacious target in >80% of the **MEDLEY** pop'n. Specific subgps of interest included extremely preterm infants <29 wks GA without CLD/CHD in Season 1, and children with CLD of prematurity or haemodynamically significant CHD in Season 1 and Season 2 in **MEDLEY**, and IC children entering their first or second season in **MUSIC**.

Extrapolation results MEDLEY: Serum conc'ns on Day 151 of both Season 1 and Season 2 in the **MEDLEY** paediatric subsets of specific interest were comparable to those in all infants in **MUSIC**. Based on the extrapolation plan agreed with the EU in the PIP, extrapolation of efficacy was demonstrated in the overall **MEDLEY** pop'n, as nirsevimab exposures were above the efficacious target (i.e. $AUC_{baselineCL}$ 12.8 mg·day/mL) in 96.7% (377/390) in the preterm cohort <35 wGA without CLD/CHD, and 89.6% (181/202) in the CLD/CHD cohort (Season 1), and 93.2% (177/190) in the CLD/CHD cohort (Season 2).

7.5. Evaluator's conclusions on clinical efficacy

The first dose-finding study in in infants was **Study 2**, which demonstrated the safety, and nAb reponse to single doses of IM nirsevimab; the 50mg IM dose was brought into **Study 3**. **Study 2** was not powered to demonstrated clinical efficacy. **Study 3** was a large international clinical efficacy trial conducted across both hemispheres, in preterm infants, a group highly vulnerable for severe RSV, entering their first RSV season. This double-blind placebo-controlled trial demonstrated a RRR of the incidence in MA RSV LRTI of 70.1% (95% CI: 52.3%, 81.2%) (p <0.0001) through 150 days post dose. However, the prespecified subgroup analysis of the primary endpoint by weight at dosing showed a significantly **lower efficacy** for the 50mg dose in infants weighing >5 kg with a RRR of incident MA RSV LRTI through 150 days post dose of 58.5% for infants >5 kg vs. >80% for infants ≤5 kg. Based on an exposure-response analysis for the primary endpoint with AUC quartiles as the exposure metric, the dosing in **Studies 4**

(MELODY), 5 (MEDLEY) and 8 (MUSIC) was amended to a fixed-dose of 50mg if body weight of the infant was <5Kg at the time of dosing, and a 100 mg dose in infants weighing ≥5 kg in Season 1. Taking into account the expected weight gain in infants when reaching their RSV Season 2, and knowing that this RSV directed mAb (with no host target) has no upper limit for toxicity a single dose of 200mg was given in the high risk populations of those with chronic lung or heart conditions entering RSV Season 2 in the **MEDLEY** study, a randomised trial with a cross over design with the active comparator mAb (palivizumab). **MELODY** was a large international randomised placebo-controlled trial, and despite the challenges posed by the COVID-19 pandemic, and the amended (reduced) sample size, the primary objective based on the Primary Cohort of **MELODY** was met. In term and late preterm infants given weight-based dosing of single dose 50mg or 100mg nirsevimab there was statistically significant clinical efficacy (RRR 74.5%; 95% CI 49.6%, 87.1%; p<0.0001) against the primary endpoint of Medically Attended RSV LRTI. The **MEDLEY** study also using weight-based dosing of single dose 50mg or 100mg IM and demonstrates that nirsevimab had comparable safety and tolerability profile to palivizumab, in the overall population, preterm infants, and those with CLD and/or CHD in Season 1, and with comparable safety findings for subjects with CLD/CHD who received nirsevimab (single IM dose of 200mg) in Season 2. However, the efficacy of the second dose was not demonstrated for reasons that include small subject numbers, and the very low rates of circulating RSV due to public health strategies to contain COVID-19. There is no evidence of immune priming in subjects who had received prior nirsevimab and no evidence that the second dose of nirsevimab boosted ADA responses in those few subjects who were ADA positive to nirsevimab in Season 1. In both seasons, based on limited data, there was no apparent impact of ADA against nirsevimab on PK and safety. In the non-randomised ongoing single-arm **MUSIC** study enrolling immunocompromised infants aged ≤24 mths, there were no new safety concerns raised in the interim analyses. The weight basing dosing in RSV season 1 was well tolerated, as was the 200mg dose in Season 2, with the caveat that numbers who received second doses were small (less than 200 subjects). There were no protocol-defined Medically Attended RSV LRTIs reported. Nirsevimab serum conc'ns were as expected based on studies in non-immuncompromised children. ADA positivity was low 3.3% with no apparent impact on safety or nirsevimab PK.

8. Clinical safety

The nirsevimab clinical development programme (**Table 5**) includes a Phase I study in adults and a Phase Ib/IIa study in preterm infants (**Section 19**), 3 complementary pivotal studies in infants and children (**Section 6 and 7**), and an open-label study in immunocompromised infants and children (**Section 7**). **Study 1** in healthy adults and **Study 2** in preterm infants born ≥32 to <35 wGA are completed single-ascending dose, safety, PK, and ADA studies. Because **Study 1** was conducted in adults and **Study 2** was a small dose-escalation study evaluating doses of 10 mg, 25 mg, and 50 mg that followed a different design, safety data from these studies are reported in the respective CSRs and detailed in **Section 19** of this report. In the completed **Study 3**, very and moderately preterm infants born ≥29 to <35 wGA received a single IM dose of 50 mg, regardless of weight at time of dosing. Based on results of this study, fixed weight-band dosing was introduced in the subsequent studies, **MELODY**, **MEDLEY** (see **Section 7.2.2**), and **MUSIC**, all 3 of these studies are ongoing.

Standard AE reporting was used; the NCI CTCAE grading scales was used. AEs were coded using MeDRA PT and SOC, in this Section on safety, these will be referred to as PT and SOC. Details of the AESI (immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopaenia) and NOCDs (=a newly diagnosed medical condition that was of a chronic, ongoing nature observed after receipt of the IP and assessed by the investigator as medically significant. Examples of NOCDs included, but were not limited to diabetes mellitus, autoimmune disease, and neurological disease are presented later in this Section.

8.1. Studies providing evaluable safety data

All the studies described above and listed in **Table 5** have provided safety data.

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

MEDLEY had safety as its sole primary outcome but because it also contributes important PK, ADA and descriptive efficacy I have chosen to detail this in **Section 7.2.2.**

8.1.2. Pivotal and/or main efficacy studies

Study 3 (**Section 6.2**) and **MELODY** (**Section 7.2.1**).

8.1.3. Other studies

8.1.3.1. Other efficacy studies

MUSIC (Section 7.3.1).

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

Study 1 and **Study 2** are detailed in **Section 19.**

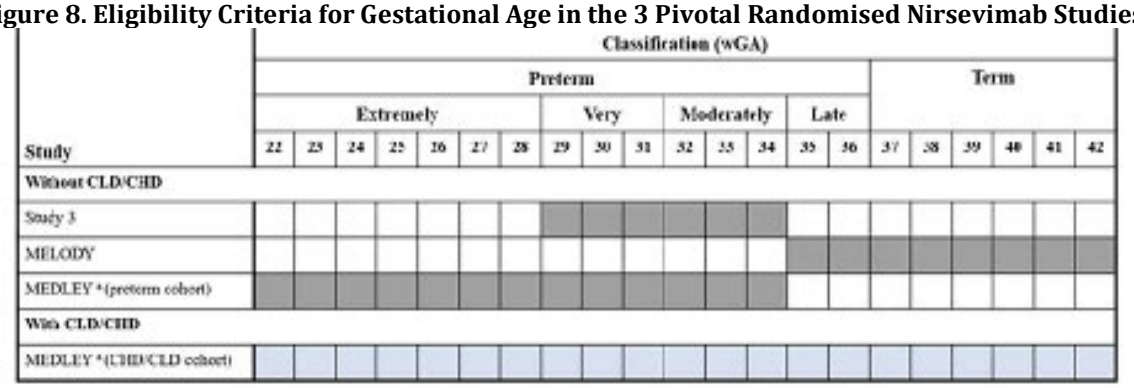
8.2. Patient exposure

Safety data are available from 3680 subjects dosed with nirsevimab (3284 subjects receiving the proposed dose). In this Section we will focus on the safety data currently available from 3620 subjects dosed with nirsevimab (with 3224 receiving the proposed dose) in the 3 complementary pivotal studies: **Study 3, MELODY, MEDLEY**. Additional safety information is available from 60 subjects dosed with nirsevimab in **MUSIC**.

Study Pop'ns: The pop'ns recruited to each of the 3 complementary pivotal studies are summarised in **Figure 8**. The following terms and age ranges (wGA at birth) were used to describe the infant pop'ns recruited to these studies:

Term: ≥37 wGA; Late preterm: ≥35 and <37 wGA; Moderately preterm: ≥32 and <35 wGA; Very preterm: ≥29 and <32 wGA; Extremely preterm: <29 wGA. The pop'n in **MUSIC** was not restricted by gestational age.

Figure 8. Eligibility Criteria for Gestational Age in the 3 Pivotal Randomised Nirsevimab Studies



[a] Palivizumab eligible, according to approved indication (SYNAGIS® PI 2021, SYNAGIS SmPC 2021) and local or national guidelines.

CHD = congenital heart disease; CLD = chronic lung disease; MEDLEY = Study D5290C00005; MELODY = Study D5290C00004; Mod = moderate; Study 3 = Study D5290C00003; wGA = weeks gestational age.

Exposure to nirsevimab: Across all studies that enrolled infants and children (**Study 2 + Study 3 + MELODY + MEDLEY + MUSIC**), 3711 subjects received nirsevimab

Table 21. Exposure in All Studies Pool – As-treated Pop'n

Treatment received	Statistics	Total
Placebo	n	1493
Palivizumab	n	304
Nirsevimab n (%)	n	3711
	10 mg	8 (0.2)
	25 mg	31 (0.8)
	50 mg	2153 (58.0)
	67 mg	1 (<0.1)
	100 mg	1485 (40.0)
	150 mg	3 (<0.1)
	200 mg	30 (0.8)

A subject who received any nirsevimab dose will be classified into nirsevimab group.
For MEDLEY, dose regimen of Season 1 is reported; if a subject received multiple nirsevimab doses in Season 1, cumulative dose is reported.
n = number of subjects in treatment group
Source: Table 2.2.1, ISA, Module 5.3.5.3

Dosing Regimens: In **Study 3**, all randomised subjects in the nirsevimab gp received a single IM dose of 50 mg, regardless of body weight. As previously described in this report, heavier infants had lower nirsevimab serum exposure, which was associated with lower efficacy. Therefore, fixed weight-band dosing (50 mg for infants weighing <5 kg or 100 mg for infants weighing ≥5 kg at the time of dosing) was introduced in **MELODY** and **MEDLEY**, and later applied in **MUSIC**. All randomised subjects in the nirsevimab gp in **MELODY** and **MEDLEY** (first season) were to receive the "proposed dose" of nirsevimab, according to the weight-band dosing regimen. For children up to 24 mths of age (**MEDLEY** and **MUSIC**) who remain vulnerable to severe RSV disease through their second RSV season, the recommended dose is 200 mg. Pooled safety analyses presented in this Section include safety and ADA data collected through Day 361 for the Primary Cohort and through at least Day 151 in the Safety Cohort in the ongoing **MELODY** study and all data in the completed Study 3 to Day 361. Safety data from **MELODY** and **Study 3** were pooled, as these studies were placebo-controlled, randomised, double-blind, studies that used the same safety endpoints and included healthy infant pop'ns. The inclusion/exclusion criteria of these 2 studies are also similar, except for GA: late preterm and term infants >35 wks 0 days GA were enrolled in **MELODY,** whilst preterm infants born between 29 wks 0 days and 34 wks 6 days GA were enrolled in **Study 3**. This GA difference does not preclude pooling the 2 studies. Studies **MELODY** and **Study 3** enrolled infants who would not be recommended to receive palivizumab per AAP or local or national guidelines. The randomised treatment gps are similar in both studies **(Table 5; and Section 6 and 7),** with subjects randomised (2:1) ratio to receive nirsevimab or placebo, stratified by hemisphere and by subject age gp at randomisation. Subjects randomised to nirsevimab received a dose of 50 mg IM for subjects with weight <5 kg at dosing or 100 mg for subjects with weight ≥5 kg at time of dosing in **MELODY**. In **Study 3**, all subjects randomised to nirsevimab received a dose of 50 mg IM. These 2 studies were thus chosen for a pooled analysis of safety. The safety data of **MEDLEY** and **MUSIC** were not pooled with **Study 3 and MELODY** and are presented in **Section 7.2.2 and Section 7.3.1** respectively. The rationale is that the **MEDLEY** study pop'n at higher risk of severe RSV disease were eligible for treatment with palivizumab and this was used as an active comparator. **MUSIC** safety data were also not pooled with the other studies because it was an open-label uncontrolled study, and in a very different paediatric pop'n of IC children at higher risk of severe RSV disease and with different background rates of AEs expected; in addition, older children were included before entering their second season. Safety data from the early phase dose-escalation studies (**Study 1 (adults) and Study 2 (dose-escalation in infants**) is detailed in **Section 19.**

Safety data are reported for the following pools:

- **MELODY (All subjects)/Study 3 (Proposed Dose) Safety Pool** (3854 subjects dosed with nirsevimab [N=2570] or placebo [N=1284]): Pooled data of all dosed subjects from **MELODY**

Primary and Safety Cohorts and dosed subjects weighing <5 kg at the time of dosing from **Study 3**. This pool only includes subjects receiving the proposed dosing scheme. This pool is a subpop'n of the following pool.
- **MELODY (All subjects)/Study 3 Safety Pool** (4441 subjects dosed with nirsevimab [N=2966] or placebo [N=1475]): Pooled data of all dosed subjects from **MELODY**, including both the Primary and Safety Cohorts, and **Study 3**. Following feedback from the FDA at the meeting on 26-Jul-2022, the 'proposed dose' pool is considered to provide the most relevant summaries of safety data to evaluate the AE profile. Two pooled safety analyses were planned and triggered by the primary and safety analyses, respectively, for **MELODY**. The 1st analysis was conducted when all subjects from the **MELODY Primary cohort** had been followed through Day 361 except for the one subject enrolled NH 2020 season who was followed through at least Day 151. All safety/ADA data collected from **Study 3** and all safety/ADA data available from the **MELODY Primary cohort** at the time of data cut-off were included in the 1st analysis. The 2nd analysis was conducted when all subjects from the **MELODY Safety cohort** had been followed through at least Day 151 and included all safety/ADA data collected from **Study 3** and all subjects in **MELODY (both Primary and Safety cohorts)** at the time of the data cut-off.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Integrated safety analyses MELODY) (All Subjects)/Study 3 (Proposed Dose) Safety Pool

In the Safety Pool of infants born at term and preterm (≥29 wGA), the percentage of subjects with AEs in the nirsevimab gp was generally comparable to those in the placebo gp across the event categories (**Table 22**). Overall, 84.0% of nirsevimab gp and 82.6% of placebo gp had at least one AE. The percentage of subjects with AEs by time post dose was generally similar in the 2 gps at each time point assessed (≤1 day, ≤3 days, ≤7 days, and ≤14, and ≤30 days post dose). Overall, the majority of AEs were graded as mild or moderate. The percentage of subjects was similar in nirsevimab and placebo gps for AEs of ≥Grade 3 severity (4.0% and 6.3%, respectively) and SAEs (7.6% and 10.5%, respectively). 9 deaths occurred through Day 361 (6 [0.2%] in the nirsevimab gp and 3[0.2%] in the placebo gp); none of the deaths was considered IP-related by the investigator, and none were known or reported to have been caused by RSV. Overall, the percentage of subjects was low and generally comparable between the nirsevimab and placebo gps for IP-related AEs (1.3% and 1.4%, respectively), investigator-assessed AESIs (0.2% and 0%, respectively, overall), IP-related skin reactions (0.6% and 0.3%, respectively), and NOCDs (0.1% and 0.3%, respectively). The AESI based on selected MedDRA PT were reported in a similar percentage of subjects in each treatment gp (23.0% and 22.6%, respectively); those considered IP-related were low and comparable between the nirsevimab and placebo gps (0.5% and 0.2%, respectively).
The percentage of subjects with AEs was generally comparable in the nirsevimab and placebo gps across the event categories. The percentage with at least one AE was 84.5% (nirsevimab gp) and 83.5% (placebo gps), and the percentage with AEs by time post dose was generally similar in the 2 gps at each time point assessed (≤1 day, ≤3 days, ≤7 days, ≤14 days, and ≤30 post dose). The nirsevimab gp vs. placebo gp had a similar percentage of subjects with AEs of ≥Grade 3 severity (4.7% and 6.6%, respectively) and SAEs (7.9% and 10.5%, respectively).
The percentages of subjects were low and generally similar between the nirsevimab and placebo gps for IP-related AEs (1.6% and 1.7%, respectively), investigator-assessed AESIs (0.3% and 0.2%, respectively), IP-related skin reactions (0.7% and 0.5%, respectively), and NOCDs (0.2% and 0.4%, respectively). AESI based on selected MedDRA PT were reported in a similar percentage of subjects in each treatment gp (23.2% nirsevimab and 22.6% placebo, respectively). The percentage of subjects with AESI based on MedDRA PT considered IP-related was low and comparable between the nirsevimab and placebo gps (0.6% and 0.3%,

respectively). One subject in the placebo gp had an IP-related SAE of fever neonatal. No IP-related NOCDs were reported.

AEs by SOC: Frequency of AEs by SOC generally similar in the 2 treatment gps. The most common AEs by SOC (>10% of subjects in either gp) reported in the nirsevimab and placebo were Infections and infestations (71.5% and 72.4%, respectively); Skin and subcutaneous tissue disorders (29.0% and 28.4%, respectively); Gastrointestinal disorders (23.8% and 24.2%, respectively); Respiratory, thoracic and mediastinal disorders (20.6% and 20.6%, respectively); and General disorders and administration site conditions (13.6% and 11.3%, respectively).The most common AEs reported by PT (>10% of subjects in either gp) with nirsevimab and placebo were URTI (31.8% and 29.9%, respectively), nasopharyngitis (19.0% and 21.0%, respectively), and pyrexia (11.8% and 10.3%, respectively).

Table 22: Overall Summary of TEAEs Through at Least 150 Days Post Dose (MELODY [All Subjects]/Study 3 [Proposed Dose] Safety Pool)

Subjects[a] with	Number (%) of Subjects[a]		
	Placebo (N=1284)	Nirsevimab (N=2570)	Total (N=3854)
At least one event	1060 (82.6)	2158 (84.0)	3218 (83.5)
Occurring ≤ 1 day post dose	14 (1.1)	50 (1.9)	64 (1.7)
Occurring ≤ 3 days post dose	68 (5.3)	151 (5.9)	219 (5.7)
Occurring ≤ 7 days post dose	170 (13.2)	316 (12.3)	486 (12.6)
Occurring ≤ 14 days post dose	309 (24.1)	632 (24.6)	941 (24.4)
Occurring ≤ 30 days post dose	505 (39.3)	1044 (40.6)	1549 (40.2)
At least one investigational product-related event	18 (1.4)	33 (1.3)	51 (1.3)
At least one event of ≥ Grade 3 severity[b]	81 (6.3)	102 (4.0)	183 (4.7)
Occurring ≤ 1 day post dose	0	0	0
Occurring ≤ 3 days post dose	2 (0.2)	4 (0.2)	6 (0.2)
Occurring ≤ 7 days post dose	5 (0.4)	9 (0.4)	14 (0.4)
Occurring ≤ 14 days post dose	8 (0.6)	14 (0.5)	22 (0.6)
Occurring ≤ 30 days post dose	17 (1.3)	23 (0.9)	40 (1.0)
At least one investigational product-related event ≥ Grade 3 severity[b]	1 (<0.1)	1 (<0.1)	2 (<0.1)
Occurring ≤ 1 day post dose	0	0	0
Occurring ≤ 3 days post dose	1 (<0.1)	0	1 (<0.1)
Occurring ≤ 7 days post dose	1 (<0.1)	1 (<0.1)	2 (<0.1)
Occurring ≤ 14 days post dose	1 (<0.1)	1 (<0.1)	2 (<0.1)
Occurring ≤ 30 days post dose	1 (<0.1)	1 (<0.1)	2 (<0.1)
Any AE with outcome death (Grade 5 severity[b])	3 (0.2)	6 (0.2)	9 (0.2)
At least one serious[c] event	135 (10.5)	195 (7.6)	330 (8.6)
At least one serious[c] and/or ≥ Grade 3 severity[b] event	143 (11.1)	208 (8.1)	351 (9.1)
At least one investigational product-related serious[c] event	1 (<0.1)	0	1 (<0.1)
At least one AESI based on investigator's assessment	0	6 (0.2)	6 (0.2)
At least one AESI based on selected MedDRA preferred term codes	290 (22.6)	590 (23.0)	880 (22.8)
At least one investigational product-related AESI based on selected MedDRA preferred term codes	3 (0.2)	13 (0.5)	16 (0.4)
At least one skin reaction	332 (25.9)	650 (25.3)	982 (25.5)
At least one investigational product-related skin reaction	4 (0.3)	15 (0.6)	19 (0.5)
At least one skin hypersensitivity reaction	0	9 (0.4)	9 (0.2)
At least one NOCD	4 (0.3)	3 (0.1)	7 (0.2)
At least one investigational product-related NOCD	0	0	0

[a] Subjects with multiple events in the same category are counted once in that category. Subjects with events in more than one category are counted once in each of those categories.
[b] Grade 3: Severe, Grade 4: Life-threatening, Grade 5: Fatal.
[c] Serious adverse event criteria: death, life-threatening, required inpatient hospitalisation, prolongation of existing hospitalisation, persistent or significant disability/incapacity, important medical event, congenital anomaly/birth defect (in the offspring of the subject).

MedDRA version 23.1.

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

Source: Table 1.3.1.1.2, ISA, Module 5.3.5.3.

AEs by Intensity: Majority of AEs were Grade 1 (59.6% of subjects with nirsevimab and 53.7% with placebo) or Grade 2 (20.4% of subjects with nirsevimab and 22.5% with placebo) in

severity. AEs of Grade 3 severity were reported in a lower percentage of the nirsevimab gp (3.5%) than the placebo gp (5.7%). Grade 4 or 5 events were infrequent, occurring in ≤1% of subjects in each gp. The most common Grade 3 AEs (>0.5% of subjects in either gp) in the nirsevimab and placebo gps were bronchiolitis (0.5% and 1.4%, respectively) and LRTI (0.4% and 0.7%, respectively). All Grade 4 AE PTs were reported in at most one subject in either treatment gp, except for LRTI in 2 (0.2%) subjects in the placebo gp. Two (0.1%) subjects in the nirsevimab gp had Grade 5 AEs of gastroenteritis, 2 (0.2%) subjects in the nirsevimab gp died, and 2 subjects in the placebo gp died of pneumonia that were not considered IP-related.

8.3.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

MEDLEY, see **Section 7.2.2**

8.3.1.3. Other studies

Other efficacy studies

MUSIC, see **Section 7.3.1.**

Studies with evaluable safety data: dose finding and pharmacology

For **Studies -1 and -2** see **Section 19.**

8.3.2. Treatment related adverse events (adverse drug reactions)

8.3.2.1. Integrated safety analyses MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool

The percentage of subjects with AEs considered IP-related to IP was low and similar between the nirsevimab and placebo gps (**Table 23**); all events were Grade 1-2 in severity with the exception of one Grade 3 severity event of rash (nirsevimab gp) reported as an investigator-assessed AESI of skin hypersensitivity in a **MELODY** subject. The most frequently reported IP-related AEs (>1 subject in either gp) were rash maculo-papular (0.3% nirsevimab; 0% placebo), irritability (0.2% nirsevimab; 0.2% placebo), pyrexia (0.1% nirsevimab; 0.2% placebo), rash (0.1% nirsevimab; 0% placebo), diarrhoea (<0.1% nirsevimab; 0% placebo), injection site pain (<0.1% nirsevimab; 0% placebo), neutrophil count decreased (0% nirsevimab; 0.2% placebo). **AE by Time Relative to Dosing:** The percentage of subjects with events within 1, 3-, 7-, 14-, and 30-days post dose was generally balanced between treatment gps. Reactogenicity measures of pyrexia and ISRs occurred at a low incidence within 1- and 7-days post dose. Within one day post dose, a low percentage of subjects had pyrexia (nirsevimab 0.2% and placebo 0.2%) and ISRs (PTs injection site pain, injection site induration, and injection site swelling [nirsevimab 0.2% and placebo 0]). Similarly, within 7 days of dosing, the percentage of subjects with these events was also low: pyrexia (nirsevimab 0.5% and placebo 0.6%) and ISRs (PTs: injection site pain, injection site induration, and injection site swelling [nirsevimab 0.3% and placebo 0%]).

Table 23. IP-Related TEAE by SOC and PT Through at Least 150 Days Post Dose (MELODY [All Subjects]/Study 3 [Proposed Dose] Safety Pool)

System organ class Preferred term (MedDRA version 23.1)	Number (%) of subjects [a]		
	Placebo (N=1284)	Nirsevimab (N=2570)	Total (N=3854)
Total number of TEAEs	23	34	57
Subjects with any TEAE	18 (1.4)	33 (1.3)	51 (1.3)
Blood and lymphatic system disorders	**2 (0.2)**	**0**	**2 (<0.1)**
Anaemia	1 (<0.1)	0	1 (<0.1)
Neutropenia	1 (<0.1)	0	1 (<0.1)
Gastrointestinal disorders	**2 (0.2)**	**2 (<0.1)**	**4 (0.1)**
Diarrhoea	0	2 (<0.1)	2 (<0.1)
Constipation	1 (<0.1)	0	1 (<0.1)
Vomiting	1 (<0.1)	0	1 (<0.1)
General disorders and administration site conditions	**4 (0.3)**	**7 (0.3)**	**11 (0.3)**
Pyrexia	3 (0.2)	3 (0.1)	6 (0.2)
Injection site pain	0	2 (<0.1)	2 (<0.1)
Decreased activity	0	1 (<0.1)	1 (<0.1)
Injection site swelling	0	1 (<0.1)	1 (<0.1)
Fever neonatal	1 (<0.1)	0	1 (<0.1)
Infections and infestations	**2 (0.2)**	**1 (<0.1)**	**3 (<0.1)**
Gastroenteritis	0	1 (<0.1)	1 (<0.1)
Pharyngitis	1 (<0.1)	0	1 (<0.1)
Upper respiratory tract infection	1 (<0.1)	0	1 (<0.1)
Injury, poisoning and procedural complications	**1 (<0.1)**	**0**	**1 (<0.1)**
Vaccination complication	1 (<0.1)	0	1 (<0.1)
Investigations	**2 (0.1)**	**1 (<0.1)**	**3 (<0.1)**
Hepatic enzyme increased	0	1 (<0.1)	1 (<0.1)
Neutrophil count decreased	2 (0.1)	0	2 (<0.1)
Metabolism and nutrition disorders	**0**	**1 (<0.1)**	**1 (<0.1)**
Decreased appetite	0	1 (<0.1)	1 (<0.1)
Nervous system disorders	**1 (<0.1)**	**2 (<0.1)**	**3 (<0.1)**
Hypersomnia	0	1 (<0.1)	1 (<0.1)
Somnolence	1 (<0.1)	1 (<0.1)	2 (<0.1)
System organ class Preferred term (MedDRA version 23.1)	**Number (%) of subjects [a]**		
	Placebo (N=1284)	**Nirsevimab (N=2570)**	**Total (N=3854)**
Psychiatric disorders	**3 (0.2)**	**4 (0.2)**	**7 (0.2)**
Irritability	3 (0.2)	4 (0.2)	7 (0.2)
Respiratory, thoracic and mediastinal disorders	**1 (<0.1)**	**1 (<0.1)**	**2 (<0.1)**
Nasal congestion	1 (<0.1)	1 (<0.1)	2 (<0.1)
Skin and subcutaneous tissue disorders	**4 (0.3)**	**15 (0.6)**	**19 (0.5)**
Rash maculo-papular	0	7 (0.3)	7 (0.2)
Rash	0	3 (0.1)	3 (<0.1)
Dermatitis	0	1 (<0.1)	1 (<0.1)
Drug eruption	0	1 (<0.1)	1 (<0.1)
Petechiae	0	1 (<0.1)	1 (<0.1)
Rash papular	1 (<0.1)	1 (<0.1)	2 (<0.1)
Skin hypopigmentation	0	1 (<0.1)	1 (<0.1)
Eczema	1 (<0.1)	0	1 (<0.1)
Erythema	1 (<0.1)	0	1 (<0.1)
Rash macular	1 (<0.1)	0	1 (<0.1)

[a] Number (%) of subjects with AEs, sorted on alphabetical order for system organ class and descending frequency order for preferred term by nirsevimab group.

Subjects with multiple events in the same preferred term are counted once in that preferred term.

Subjects with events in more than one preferred term are counted once in each of those preferred terms.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activity; N = number of subjects; TEAE = treatment-emergent adverse event.

Source: Table 1.3.3.1.2, ISA, Module 5.3.5.3.

8.3.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

MEDLEY, see **Section 7.2.2**

8.3.2.3. Other studies

Other efficacy studies

MUSIC, see **Section 7.3.1.** For **Studies -1 and -2** see **Section 19.**

8.3.3. Deaths and other serious adverse events

None of the deaths in these 4 studies were considered to be IP-related by the investigator, and none was known or reported to have been caused by RSV.

8.3.3.1. Integrated safety analyses (MELODY) (All Subjects)/Study 3 (Proposed Dose) Safety Pool

Nine deaths (6 subjects [0.2%] in the nirsevimab gp and 3 subjects [0.2%] in the placebo gp) were reported. In **Study 3**, one additional death (due to acute bronchopneumonia) occurred in the placebo gp 6 days after end (Day 367). The event was considered not related to IP. In **MELODY (Primary cohort),** one additional death (due to a road traffic accident; not associated with an AE) occurred in the nirsevimab gp after Day 361 (on Day 440). In addition, one subject was enrolled and failed screening and died due to *Streptococcal* meningitis without receiving IP. The frequency of SAEs was slightly lower in the nirsevimab gp vs. placebo gp (7.6% and 10.5%, respectively). The most frequently reported events in both treatment gps occurred in the SOC of Infections and infestations (5.5% nirsevimab gp and 8.6% placebo gp). The percentage of subjects with individual PTs was generally balanced between the treatment gps. The most frequently reported SAEs (>1% in either treatment gp) by PT with nirsevimab (and placebo) was bronchiolitis (1.3% and 2.6%, respectively).
Four subjects in the nirsevimab gp and 0 subjects in the placebo gp had an SAE of febrile convulsions. All cases were considered not IP-related to IP. All of the cases were confounded by concomitant infectious diseases. No IP-related SAEs were reported in the nirsevimab gp. One subject in the placebo gp had an IP-related SAE of fever neonatal. No subjects had an SAE within 1 day post dose. Within 7-, 14-, and 30-days post dose, a similar percentage in both treatment gps had an SAE. The percentage of subjects with SAEs was similar in the placebo gp compared with the nirsevimab gp (10.5% and 7.9%). The most frequently reported events in both treatment gps occurred in the SOC of Infections and infestations (5.9% nirsevimab gp and 8.7% placebo gp). The percentage of subjects with individual PTs was generally balanced between treatment gps. The most frequently reported (>1% in either treatment gp) SAEs by PT with nirsevimab and placebo was bronchiolitis (1.5% and 2.6%, respectively). No IP-related SAEs were reported in the nirsevimab gp. One subject in the placebo gp had an IP-related SAE of fever neonatal. No subjects had an SAE within 1 day post dose. Within 7-, 14-, and 30-days post dose, a similar percentage of subjects in both treatment gps had an SAE.

8.3.3.2. Main/pivotal studies that assessed safety as the sole primary

MEDLEY (see also **Section 7.2.2**). **MEDLEY** subjects were randomised 2:1 to nirsevimab or palivizumab in Season 1, 5 subjects (0.8%) in the nirsevimab gp and 1 subject (0.3%) in the palivizumab gp had an AE that resulted in death; these subjects had serious complex underlying medical conditions. In Season 2, no AEs resulted in death.
Overall Pop'n, Preterm and CLD/CHD Cohorts in RSV <u>Season 1</u>: In the overall pop'n, the frequency of SAEs was similar between the nirsevimab and palivizumab gps (13.0% vs. 12.5%, respectively). SAEs were most frequently reported (>2% of subjects in either the nirsevimab or palivizumab gp) in the SOCs of infections and infestations (8.3% vs. 6.6%, respectively). The most common SAEs (>2 subjects) reported for nirsevimab (vs. palivizumab) were bronchiolitis (12 vs. 4 subjects), gastroenteritis (5 vs. 1 subject), bronchitis (5 vs. 2 subjects, respectively), pneumonia (5 vs. 1 subject, respectively), RSV bronchiolitis (4 vs. 2 subjects, respectively), COVID-19, and viral URTI (3 vs. 1 subject each, respectively). Within 1, 3-, 7-, 14-, and 30-days

post first dose, a similar percentage in the nirsevimab and palivizumab gps had an SAE. The incidence of SAEs was also balanced between the nirsevimab and palivizumab gps in the preterm (8.6% vs. 6.3%, respectively) and CLD/CHD (21.6% vs. 25.5%, respectively) cohorts. However, the frequency of events was higher in the CLD/CHD cohort than the preterm cohort. This difference likely due to a notably higher event rate in the infections and infestations SOC in the CLD/CHD cohort compared with the preterm cohort. No SAEs considered to be IP-related.
<29 wGA, CLD, and CHD Subpop'ns: Frequency of SAEs generally similar between the treatment gps in each Subpop'n (18.0% vs. 19.1% for the <29 wGA subpop'n, 14.4% vs. 19.1% for the CLD subpop'n, and 35.7% vs 36.4% for the CHD subpop'n, for nirsevimab vs. palivizumab, respectively). None considered by the Investigator to be IP-related.
Overall (CLD/CHD Cohort) and CLD and CHD Pop'ns in RSV Season 2 CLD/CHD Cohort
Incidence of SAEs low overall but numerically higher in the NIRS/NIRS and PALI/NIRS gps than in the PALI/PALI gp (9.4% vs. 10.0% vs. 0% for NIRS/NIRS, PALI/NIRS, and PALI/PALI, respectively); however, this was not observed within all analysed time points through 30 days post first dose. SAEs were most frequently reported (>2% of subjects in any treatment gp) 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 gp) 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), LRTI (2 vs. 1 vs. 0 subjects, respectively), and URTI (2 vs. 0 vs. 0 subjects, respectively). None of the SAEs was considered by the Investigator to be IP-related. No subjects in any treatment gp 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 gps, respectively, had an SAE.
CLD and CHD Subpop'ns: The incidence of SAEs was generally low in treatment gps across the individual CLD and CHD subpop'ns. In both subpop'ns, the incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS gps than in the PALI/PALI gp (9.8% vs. 8.0% vs. 0% for the CLD subpop'n and 8.9% vs. 14.3% vs. 0% for the CHD subpop'n, for NIRS/NIRS, PALI/NIRS, and PALI/PALI, respectively). No SAEs considered to be IP-related.

8.3.3.3. Other studies

Other efficacy studies

MUSIC, see also **Section 7.3.1.** In **MUSIC**, one subject (1.7%) experienced an AE of tumour haemorrhage with an outcome of death. In addition, one subject was enrolled, failed screening, and died from septic shock secondary to typhlitis and *Stenotrophomonas* bacteraemia without receiving IP. In **MUSIC**, 18 subjects (30.0%) reported 36 SAEs. All SAEs were reported in ≤2 subjects (3.3%) each. No subjects reported a TESAE within 1 day of dosing; within 3 days of dosing, 1 subject (1.7%) reported 1 TESAE; within 7 days of dosing, 2 subjects (3.3%) reported 2 TESAEs; within 14 days of dosing, 3 subjects (5.0%) reported 3 TESAEs; and within 30 days of dosing, 5 subjects (8.3%) reported 6 TESAEs.

Studies with evaluable safety data: dose finding and pharmacology

For **Studies -1 and -2** see **Section 19.**

8.3.4. Discontinuations due to adverse events

As subjects received a single dose of IP in **Study 3, MELODY, and MUSIC**, discontinuation of IP due to AE was not possible. In **MEDLEY**, one subject (0.2%) in the nirsevimab gp discontinued IP due to an AE associated with a placebo IP dose. Across the 4 studies, there were no discontinuations from the study due to an AE in dosed subjects.

8.4. Evaluation of issues with possible regulatory impact

8.4.1. Liver function and liver toxicity, renal function and renal toxicity, haematological parameters and haematological toxicity

Clinical lab data were collected **only** from sites in Japan in **MELODY, MEDLEY**, and **MUSIC** and **not pooled** across studies. There were no trends or clinically meaningful changes from baseline in haematology or hepatic or renal chemistry. Evaluation of lab-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 gps overall or by PT in the pivotal studies. Lab associated AEs in these SOCs were consistent with those expected for a pop'n of IC infants and children.

8.4.2. Electrocardiograph findings and cardiovascular safety

Not Applicable.

8.4.3. Vital signs and clinical examination findings

Vital signs were collected at the time points specified in the protocols (see **Module 5**) results are presented by subject in the individual CSRs (see Listing 16.2.9.a, **MELODY** iCSR, Module 5.3.5.1; Listing 16.2.9, **Study 3** CSR, Module 5.3.5.1, and Listing 16.2.9.1 and Listing 16.2.9.2 for RSV Season 1 and 2, **MEDLEY** iCSR, Module 5.3.5.1). No clinically meaningful changes seen.

8.4.4. Immunogenicity and immunological events

Antibody-Dependent Enhancement: This was explored in depth as a known complication of this class of therapeutic agent. To date, there are no data to support the occurrence of ADE of RSV disease following administration of nirsevimab. Several nonclinical studies were conducted to assess the potential risk of ADE following administration of nirsevimab (**Section 1.1.4 and Section 2.5 of Module 2.6.2**). Since a severe clinical presentation can occur with the natural RSV infection and there are no biomarkers to distinguish this, clinical study assessment entails comparison of frequency of severe cases in intervention and control gps (Arvin). In clinical studies the most serious concern of enhanced disease upon first natural infection with RSV was excluded. In the **MELODY Primary Cohort/Study 3 (proposed dose) pool**, high protection against hospitalisation with MA RSV LRTI (RRR vs. placebo: 77.3%; 95% CI 50.3% to 89.7%) and against very severe MA RSV LRTI (RRR vs. placebo: 86.0%; 95% CI 62.5% to 94.8%) through Day 151 was observed. Furthermore, there was a trend for hospitalised cases of RSV LRTI to be less severe in nirsevimab recipients than placebo recipients.
Another theoretical concern is the potential of enhanced disease in the setting of low serum conc'ns of mAb when the natural infection occurs associated with pathogenic immune complexes (anti-viral mAb and virions), and this could manifest as the serum conc'n of mAb declines. Exploratory efficacy from **MELODY Primary Cohort** for South African subjects who were first exposed to RSV 5 mths after IP dosing, showed a trend toward reduced MA RSV LRTI for nirsevimab vs. placebo when evaluated from Day 151 through Day 361 (hazard ratio 0.491; 95% CI 0.158 to 1.523). Data collection to further support evaluation of disease experience in the setting of low levels of nirsevimab in the second year is available for **MELODY Primary Cohort** from Day 362-511 and is ongoing in the **MELODY Safety Cohort**.
In **MELODY** Primary Cohort results from Day 362 to Day 511, rates of any MA LRTI due to RSV confirmed by central or local test (All MA RSV [any test] LRTI) were low and balanced across treatment gps (nirsevimab vs. placebo; 8/964 subjects [0.8%] vs. 4/482 subjects [0.8%]). Two events of MA RSV bronchiolitis were reported that required hospitalisation (all MA RSV [any test] respiratory illness with hospitalisation). The 2 events were 483 days post initial dose in a set of twins, of which one was administered nirsevimab and the other placebo. The events for remaining subjects in both treatment gps were managed in the outpatient setting. In summary, safety results from the 2nd season (Day 362-511) in the **MELODY** Primary Cohort do not show

any increase in cases of MA RSV LRTI and no increased severity of disease for infants administered nirsevimab compared to infants administered placebo.

Effect of Anti-Drug Antibody Status: Data on the evaluation of immunogenicity and its impact on safety are available to Day 361 for **MEDLEY RSV Season 1** and to at least Day 151 for the **MELODY (All subjects)/Study 3 pooled pop'ns**, **MEDLEY RSV Season 2**, and **MUSIC**. ADA positivity is defined as a titre of ≥50 for nirsevimab (**See also Integrated Summary of Immunogenicity, Module 5.3.5.3).** Across the 3 complementary pivotal studies and **MUSIC**, the percentage of subjects who were ADA-positive to nirsevimab anytime post-baseline through Day 361 was low: 4.7% (117/2482) subjects in the nirsevimab gp in the **MELODY (All Subjects)/Study 3 Safety Pool** and 4.9% (141/2864) subjects in the nirsevimab gp in the **MELODY (All Subjects)/Study 3 Safety Pool** (based on available assessments anytime through Day 361 for the **MELODY** Primary Cohort and **Study 3**, and through at least Day 151 for the **MELODY** Safety Cohort), and 34/587 (5.8%) subjects in the nirsevimab gp in **MEDLEY** Season 1 (24 in preterm and 10 in CLD/CHD cohorts).

In **MEDLEY RSV Season 2**, for the 180 CLD/CHD subjects in the NIRS/NIRS gp in Season 2 with available serum samples for testing, ADA was detected in 7/173 (4.0%) subjects at Day 361 of Season 1. At Day 31 and Day 151 of Season 2, ADA was detected in 1/90 (1.1%) and 0/158 (0.0%) subjects, respectively, showing that there was **no** immune priming in subjects by receipt prior nirsevimab. All subjects with any post-baseline ADA in Season 1 had no detectable ADA in Season 2, showing that the second nirsevimab dose (Season 2 Day 1) did not boost the immune response to nirsevimab. Notably, no hypersensitivity (or other AESI) was reported in Season 2 for this gp of subjects who received a second dose in Season 2 or in any treatment gp. For subjects who received nirsevimab in Season 2 after palivizumab in Season 1 (PALI/NIRS), post-baseline ADA against nirsevimab in Season 2 was detectable in 1 (of 40) subject; there were no IP-related AEs, AESIs, skin hypersensitivity reactions for this subject.

In **MUSIC**, 3.3% (2/60) of subjects were ADA-positive post-baseline; both subjects received the first dose of nirsevimab in their second season and were ADA-positive at Day 361. There were no IP-related AEs, AESIs, or skin hypersensitivity reactions in either of these 2 subjects.

Overall, although the nos. of subjects in the nirsevimab gp who were ADA-positive post-baseline was small and data were limited, ADA did not appear to impact the safety of nirsevimab. Across the pivotal studies, subjects in the nirsevimab gp who were positive for ADA post-baseline had a similar safety profile compared to those who were negative for ADA post-baseline or to comparator gps. No safety concerns were noted for 2 subjects with postbaseline ADA in the open-label **MUSIC** study.

With respect to AEs of potential concern in the presence of ADA, a single nirsevimab subject with investigator-assessed skin hypersensitivity reactions had detectable post-baseline ADA to nirsevimab at Day 361; the skin hypersensitivity event of contact dermatitis occurred well beyond the expected time frame for immediate hypersensitivity in a **MEDLEY** CLD/CHD Cohort in RSV Season 1 and was considered unrelated to IP. There have been no reports of investigator assessed immune complex disease across the studies and the single subject in **MUSIC** with immune complex disease based on PT (an AE representing worsening of an underlying condition present at baseline) had no ADA detectable post-baseline.

MELODY (All Subjects)/Study 3 (Proposed dose) Safety Pool: Overall, 117 (4.7%) nirsevimab subjects and 17 placebo subjects (1.4%) were ADA-positive to nirsevimab post-baseline. Of these 117, 112 (95.7%) subjects reported an AE and of the 17 placebo subjects who were ADA-positive post-baseline, 14 (82.4%) subjects reported an AE. Of 2453 subjects who did not have any ADA-positive post-baseline, 2044 (83.3%) reported AEs and of the 1267 placebo subjects who were ADA-positive post-baseline, 1046 (82.6%) subjects reported an AE. The most frequently reported AEs (>10%) among nirsevimab subjects who were ADA-positive post-baseline (vs. those who did not have any ADA-positive post-baseline) were: URTI (58/117 [49.6%] subjects and 757/2453 [30.9%] subjects, respectively);gastroenteritis (22/117 [18.8%] subjects and 222/2453 [9.1%] subjects, respectively); rhinitis (20/117 [17.1%] subjects and 209/2453 [8.5%] subjects, respectively); dermatitis diaper (nappy) (19/117

[16.2%] subjects and 237/2453 [9.7%] subjects, respectively); nasal congestion (19/117 [16.2%] subjects and 189/2453 [7.7%] subjects, respectively); diarrhoea (16/117 [13.7%] subjects and 174/2453 [7.1%] subjects, respectively); bronchiolitis (15/117 [12.8%] subjects and 154/2453 [6.3%] subjects, respectively).
14 (12.0%) subjects positive for ADA post-baseline reported SAEs and 181 (7.4%) subjects without ADA-positive post-baseline reported SAEs. No trends by PT were identified for subjects positive for ADA post-baseline compared to subjects without ADA-positive post-baseline.
MEDLEY Season 1 and Season 2: Different assays for ADA against nirsevimab and palivizumab were used, hence ADA incidence and titres cannot be directly compared.
MEDLEY Season 1 Immunogenicity and Safety: Through Day 361 for Season 1, 86.8% of the overall study pop'n had samples available for ADA assessment at Day 361. Of the subjects who had serum samples available for testing during RSV Season 1, ADA to nirsevimab was detected post-baseline in 5.8% of subjects (34/587) in the nirsevimab gp (24 in preterm and 10 in CLD/CHD cohorts) and ADA to palivizumab in 6.9% of subjects (20/289) in the palivizumab gp (14 in preterm and 6 in CLD/CHD cohorts). In Season 1, 79.4% (27/34) and 71.9% (417/580) nirsevimab subjects with nirsevimab ADA-positive post-baseline and without nirsevimab ADA-positive post-baseline, respectively, had at least one AE. The most frequently reported AEs in nirsevimab ADA-positive subjects vs. nirsevimab ADA-negative subjects were: URTI (13/34 [38.2%] subjects and 135/580 [23.3%] subjects, respectively), cough (5/34 [14.7%] subjects and 11/580 [1.9%] subjects, respectively), and RSV bronchiolitis (4/34 [11.8%] subjects and 2/580 [0.3%] subjects, respectively). Similar results reported across preterm and CLD/CHD cohorts in Season 1. 8 (23.5%) subject ADA-positive to nirsevimab post-baseline had SAEs and 72 (12.4%) subjects without ADA-positive to nirsevimab post-baseline had SAEs in Season 1.
MEDLEY Season 2 Immunogenicity and Safety: In Season 2, 88.2% of subjects in the CLD/CHD cohort had at least one sample available for ADA assessment at Season 2 Day 151 (158/180 [87.8%] in the NIRS/NIRS gp, 37/40 [92.5%] in the PALI/NIRS gp, and 36/42 [85.7%] in the PALI/PALI gp), and 37.0% of subjects in the CLD/CHD cohort had samples available for ADA assessment at Season 2 Day 361 (66/180 [36.7%] in the NIRS/NIRS gp, 17/40 [42.5%] in the PALI/NIRS gp, and 14/42 [33.3%] in the PALI/PALI gp). For the CLD/CHD subjects in the NIRS/NIRS gp 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. Limited data were available for Day 361 (66 subjects); therefore, data are likely to change at final analysis. These data show that there was **no immune priming** in subjects by receipt of a prior nirsevimab dose **or** boosting of an anamnestic response based on their Season 1 and Season 2 immunogenicity data: For subjects who received nirsevimab in Season 2 after receiving palivizumab in Season 1 (PALI/NIRS), post-baseline ADA against nirsevimab in Season 2 was detectable in 2.5% (1/40) of subjects with available samples; there were no IP-related AEs, AESIs, or skin hypersensitivity reactions for this subject.
MUSIC: 3.3% (2/60) subjects were ADA-positive post-baseline; both subjects received the first dose of nirsevimab in their second season and were ADA-positive at Day 361. There were no IP-related AEs, AESIs, or skin hypersensitivity reactions in either of these 2 subjects.

8.4.5. Serious skin reactions

Skin Reactions and Skin Hypersensitivity Reactions Overview of Skin Reactions and Skin Hypersensitivity Reactions across Studies
AEs that involved the skin and subcutaneous tissues were collected as skin reactions, with a few exceptions for skin reactions that could be definitively diagnosed such as impetigo, varicella, and scabies or isolated skin lesions (single papule, macule, or insect bite). Detailed information was collected on a dedicated skin reaction case report form (CRF). Additionally, investigators were asked to assess whether the skin reaction was a hypersensitivity/allergic reaction and to provide their own assessment of aetiology. In **MUSIC**, CRF guidelines specified reporting of skin reactions as skin hypersensitivity regardless of causality and for the 3 complementary pivotal studies only if the investigator considered the event IP-related.

In summary, across the 4 studies, >15% of the study pop'ns had any skin reaction reflecting the common occurrence of skin rashes, in this age gp. Skin reactions were generally balanced between nirsevimab and comparator gps without any particular trend by PT, across the pivotal studies, and no safety signal was identified by PT in the open-label **MUSIC** study. There was a low incidence of IP-related skin reactions (≤0.6%) and the percentage of subjects with IP-related skin reactions was balanced between nirsevimab and comparator gps across the pivotal studies for infants entering their first RSV season based on results through 360 days post dose in the **MELODY (All subjects)/Study 3 pooled pop'ns** and **MEDLEY RSV Season 1**. There were no IP-related skin reactions in **MEDLEY RSV Season 2** in any treatment gp. Consistent with these findings, two subjects had an IP-related skin reaction in the immunocompromised pop'n in **MUSIC**. Investigator-assessed skin hypersensitivity reactions also occurred with a low frequency across studies. In the **MELODY (All subjects)/Study 3 (proposed dose)** and **MELODY** (All subjects)/**Study 3** pools, 0.2% (9/3854; nirsevimab 0.4% [9/2570], placebo 0.0% [0/1284]) of subjects and 0.3% (15/4441; nirsevimab 0.4% [12/2966], placebo 0.2% [3/1475]) of subjects, respectively, had skin hypersensitivity events. However, 4 events reported as skin hypersensitivity reactions in 4 subjects who received nirsevimab were clinically inconsistent with hypersensitivity, based on their nature and latency of onset after dosing. In **MEDLEY RSV Season 1**, skin hypersensitivity reactions were reported in 2 (0.2%) subjects in the nirsevimab gp through 360 days post first IP dose; however, no skin hypersensitivity reactions were reported within 30 days post first IP dose in RSV Season 1 or through at least 150 days post first IP dose in RSV Season 2 in any treatment gp. Notably no such events occurred in 180 subjects who received a second dose of nirsevimab in Season 2 (NIRS/NIRS gp) who were at theoretical risk of increased hypersensitivity, having been exposed to nirsevimab previously in Season 1. Of the 60 immunocompromised infants and children dosed with nirsevimab in their first or second RSV season in MUSIC, one subject had an IP-related skin hypersensitivity reaction.
Across studies, only 1 subject with investigator assessed skin hypersensitivity reactions had detectable ADA to nirsevimab post-baseline. For this subject in the CLD/CHD cohort in **MEDLEY** RSV Season 1, ADA was detected at Day 361 with negative results at the baseline, Day 31, and Day 151 visits; and the skin hypersensitivity event of contact dermatitis occurred well beyond the expected time frame for immediate hypersensitivity, was considered unrelated to IP, and was not reported as an AESI.
MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool: The percentage with IP-related skin reactions was low, occurring in 0.6% (15/2570) subjects in the nirsevimab gp and 0.3% (4/1284) subjects in the placebo gp (**Table 24**). In the nirsevimab gp, rash maculo-papular (7 [0.3%] subjects) and rash (3 [0.1%] subjects) were the only PTs occurring in >1 subject. In the placebo gp, no events occurred in >1 subject. No events were considered to meet the criteria for SAEs. Of the IP-related skin reactions, 6 subjects in the nirsevimab gp (PT rash in 2 subjects; PT petechiae in 1 subject; PT rash maculopapular in 2 subjects; PT rash papular in 1 subject) and 0 subjects in the placebo gp were considered skin hypersensitivity reactions and reported as AESIs by investigator assessment. The remaining IP-related skin reactions comprised an event of injection site swelling (in the nirsevimab gp) and rashes, none of which was characterised as urticarial or involving angioedema in either treatment gp whether they occurred on Day 1 or later. In the nirsevimab and placebo gps, 0.2% and <0.1% of subjects, respectively had IP-related skin reaction events within one day, 0.4% and 0.2% of subjects, respectively, had IP-related skin reaction events within 3 days, 0.5% and 0.2% of subjects, respectively, had IP-related skin reaction events within 7 days, 0.5% and 0.3% of subjects, respectively, had IP-related skin reaction events within 14 days, and 0.5% and 0.3% of subjects, respectively, had skin reaction events within 30 days.

Table 24. IP-Related TE Skin Reactions by SOC and PT Through at Least 150 Days Post Dose (MELODY [All Subjects]/Study 3 [Proposed Dose] Safety Pool)

System organ class Preferred term (MedDRA version 23.1)	Number (%) of subjects [a]		
	Placebo (N=1284)	Nirsevimab (N=2570)	Total (N=3854)
Total number of TEAEs	4	15	19
Subjects with any TEAE	4 (0.3)	15 (0.6)	19 (0.5)
General disorders and administration site conditions	**0**	**1 (<0.1)**	**1 (<0.1)**
Injection site swelling	0	1 (<0.1)	1 (<0.1)
Skin and subcutaneous tissue disorders	**4 (0.3)**	**14 (0.5)**	**18 (0.5)**
Rash maculo-papular	0	7 (0.3)	7 (0.2)
Rash	0	3 (0.1)	3 (<0.1)
Dermatitis	0	1 (<0.1)	1 (<0.1)
Drug eruption	0	1 (<0.1)	1 (<0.1)
Petechiae	0	1 (<0.1)	1 (<0.1)
Rash papular	1 (<0.1)	1 (<0.1)	2 (<0.1)
Eczema	1 (<0.1)	0	1 (<0.1)
Erythema	1 (<0.1)	0	1 (<0.1)
Rash macular	1 (<0.1)	0	1 (<0.1)

[a] Number (%) of subjects with AEs, sorted on alphabetical order for system organ class and descending frequency 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 terms.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects;
TEAE = treatment-emergent adverse event.
Source: Table 1.4.3.1.2, ISA, Module 5.3.5.3

8.4.6. Other safety parameters – injection site reactions (ISRs)

Study 2 and **MUSIC**: no local ISRs occurred. A summary of ISRs is provided for **MELODY**, **Study 3**, and **MEDLEY** by treatment gp and by dose in **Module 2.7.4 Summary of Clinical Safety, Table 43-45**, respectively. All ISRs across the complementary pivotal studies were Grade 1 nonserious events.

8.4.7. Other safety parameters – AESI

AESIs for the nirsevimab clinical development programme included immediate hypersensitivity (including anaphylaxis), immune complex disease, and thrombocytopaenia. Across studies, AESIs based on investigator assessment were reported in very few subjects, none were reported as an SAE, and none of the subjects had any post-baseline ADA detected with samples available for analysis. AESIs assessed as skin hypersensitivity comprised all 12 events in the **MELODY/Study 3 pooled pop'ns** (9 of which were in the nirsevimab gp, all considered IP-related) and 5 events in the **MUSIC** study (of which 1 of 5 were considered IP-related), and one event in **MEDLEY** RSV Season 1. AESIs of thrombocytopaenia comprised the remaining 2 events in **MEDLEY** RSV Season 1, both considered unrelated to IP. No AESIs were reported in **MEDLEY** RSV Season 2.

MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool: Overall, the percentage of subjects with AESIs by investigator assessment was low, occurring in 6 (0.2%) subjects in the nirsevimab gp and 0 subjects in the placebo gp (**Table 25**). Rash (2 [< 0.1%] subjects) and rash maculo-papular (2 [< 0.1%] subjects) were the only events that occurred in >1 subject. All events were considered by the investigator to be skin hypersensitivity reactions related to IP and no events were reported as SAEs. All rash events within 7 days of IP dosing and the petechiae occurred >30 days post dose. All events were assessed as Grade 1 in severity with the exception of one event of rash in the nirsevimab gp from the **MELODY** study (Primary Cohort) reported as a Grade 3 severity event the rash was characterised as generalised, macular, and

without systemic features with onset 6 days post dose and of 20 days duration. The onset of this event is not consistent with immediate hypersensitivity. None of the subjects in the nirsevimab gp with investigator-assessed AESIs had any ADA to nirsevimab detectable post-baseline for available assessments. No AESIs of thrombocytopaenia were reported, however, one event of thrombocytopaenia was reported as an AE and 1 event of petechiae was reported as an AESI of hypersensitivity. No events of immune complex disease reported.

Table 25. TE AESI based on Investigator Assessment by SOC and PT Through at Least 150 Days Post Dose (MELODY [All Subjects]/Study 3 [Proposed Dose] Safety Pool)

System organ class Preferred term (MedDRA version 23.1)	Number (%) of subjects [a]		
	Placebo (N=1284)	Nirsevimab (N=2570)	Total (N=3854)
Total number of TEAEs	0	6	6
Subjects with any TEAE	0	6 (0.2)	6 (0.2)
Skin and subcutaneous tissue disorders	**0**	**6 (0.2)**	**6 (0.2)**
Rash	0	2 (<0.1)[b]	2 (<0.1)
Rash maculo-papular	0	2 (<0.1)[c]	2 (<0.1)
Petechiae	0	1 (<0.1)[d]	1 (<0.1)
Rash papular	0	1 (<0.1)[e]	1 (<0.1)

[a] Number (%) of subjects with AEs, sorted on alphabetical order for system organ class and descending frequency order by total column.
[b] Subject 20033410001 in Study 3 and Subject 20042700001 in MELODY Primary Cohort; events were recorded as skin hypersensitivity reactions and were considered IP-related by the investigator (Section 2.1.6.1).
[c] Subjects 20046180004 and 20048670072 in MELODY Safety Cohort; events were recorded as skin hypersensitivity reactions and were considered IP-related by the investigator (Section 2.1.6.1).
[d] Subject 20032910003 in Study 3; event was recorded as skin hypersensitivity reactions and was considered IP-related by the investigator (Section 2.1.6.1).
[e] Subject 20048720096 in the MELODY Safety Cohort (Section 2.1.6.1); event was recorded as skin hypersensitivity reactions and was considered IP-related by the investigator

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 one preferred term are counted once in each of those preferred terms.
AE = adverse event; IP = investigational product; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; TEAE = treatment-emergent adverse event.
Source: Table 1.4.2.1.2, ISA, Module 5.3.5.3

8.5. Other safety issues

8.5.1. Safety in special pop'ns

Infants and children at higher risk for severe RSV disease: Safety evaluated in **MEDLEY** in 918 infants at higher risk for severe RSV disease, including 196 extremely preterm infants (GA <29 wks) and 306 infants with CLD, or CHD entering their first RSV season, who received nirsevimab (614 infants) or palivizumab (304 infants). The safety profile of nirsevimab in infants who received nirsevimab in their first RSV season was comparable to the palivizumab comparator and consistent with the safety profile in term and preterm infants born ≥29 wGA (**MELODY** [All Subjects]/**Study 3** Safety Pool). Safety was evaluated in **MEDLEY** in 220 children with CLD or CHD who received nirsevimab or palivizumab in their first RSV season and went on to receive nirsevimab entering their second RSV season. The safety profile of nirsevimab in children who received nirsevimab in their first and second RSV season (N = 180) was comparable to that in children who received palivizumab in their first RSV season and then nirsevimab in their second RSV season (N=40). The safety profile of nirsevimab in these children from both arms was consistent with the safety profile in term and preterm infants GA ≥29 wks (**MELODY** [All Subjects]/**Study 3** Safety Pool) and comparable to children who received palivizumab for both RSV seasons. Safety was also evaluated in **MUSIC**, an open-label, uncontrolled, single-dose trial in 60 IC infants and children ≤24 mths, who received nirsevimab in their first or second RSV season. Subjects had ≥1 of the following: immunodeficiency (combined, antibody, or other aetiology) (28); systemic highdose corticosteroid therapy (17); organ or bone marrow transplantation (12); receiving immunosuppressive chemotherapy (9);

other immunosuppressive therapy (9), and HIV infection (1). The safety profile of nirsevimab was consistent with that expected for a pop'n of IC children and with the safety profile in term and preterm infants GA ≥29 wks **(MELODY [All Subjects]/Study 3 Safety Pool)**.

Intrinsic Factors

Effect of Age - Neonates (<28 Days at Randomisation) -MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool: 855 subjects were included in the subgp analyses for neonates including 564 subjects who received nirsevimab. All 564 neonates dosed with nirsevimab in these studies received the proposed dose. The percentage with AEs in each event category were generally comparable between the nirsevimab gp and placebo gp. The percentage with AESIs by MedDRA PT within 1, 3-, 7-, 14-, and 30-days post dose was also comparable. The percentage with AEs (nirsevimab 79.3% and placebo 77.0% of neonates) and SAEs (nirsevimab 12.9% and placebo 10.7% of neonates) were both generally balanced between treatment gps with no clinically meaningful imbalance by SOC or PT. The percentage with IP-related AEs was low and generally comparable between the nirsevimab and placebo gps (0.5% and 0.7% of neonates, respectively). There were no NOCDs in neonates. In neonates in **MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool**, nirsevimab has an AE profile similar to the overall pop'n in MELODY (All Subjects)/Study 3 Safety Pool with a general balance between nirsevimab and placebo gps in the type and frequency of AEs and no clinically meaningful imbalance between treatment gps for AEs and SAEs by SOC or PT.

MEDLEY Season 1: Safety data for higher risk neonates in the first RSV season is available for 75 neonates in **MEDLEY**, including 46 subjects dosed with nirsevimab (40 in Preterm cohort and 6 in CLD/CHD cohort) and 29 subjects dosed with palivizumab (22 in Preterm cohort and 7 in CLD/CHD cohort). Through 360 days post first dose in **MEDLEY**, the data patterns observed for neonates were consistent with the overall study pop'n, with similar types and frequencies of AEs between the nirsevimab and palivizumab gps. The incidences of AEs, ≥ Grade 3 AEs, and SAEs were numerically lower in the nirsevimab gp than the palivizumab gp in neonates. There was one AE with an outcome of death (a subject in the palivizumab gp in the CLD/CHD cohort) in neonate subjects. No IP-related events were reported in either treatment gp. No NOCDs occurred in either treatment gp. Findings were similar for the overall summary of AEs through 30 days post first dose. The numerical difference in nos. of events reported for the SOC skin and subcutaneous tissue disorders was primarily driven by more events of dry skin and eczema (all unrelated of Grade 1 to 2 severity) in the nirsevimab gp compared to the palivizumab gp.

Age at Randomisation (≤3.0 Mths, >3.0 to ≤6.0 Mths, and >6.0 Mths): Safety by subgps of age at randomisation was analysed only for the **MELODY (Primary Cohort)/Study 3 (Proposed Dose) Safety Pool**, **MELODY (Primary Cohort)/Study 3 Safety Pool** (**see Table 1.3.1.2.2, Appendix 2.7.4.8.3 ISA first analysis Module 5.3.5.3**) and **MEDLEY RSV Season 1**. Since no notable difference in safety was observed between age gps used as randomisation stratum at 1st analysis, AEs were not summarised by age gps used as randomisation stratum at 2nd analysis for **MELODY (All subjects)/Study 3 (Proposed dose)** and **MELODY** (All subjects)/Study 3 safety pools. For the **MELODY (Primary Cohort)/Study 3 (Proposed Dose) Safety Pool**, AE rates in each event category for the nirsevimab gp were generally comparable to the placebo gp for the 3 age subgps. In all age subgps, placebo had a slightly higher percentage with SAEs. For nirsevimab, AE rates for each event category were similar across the age gps. Results consistent for **MELODY (Primary Cohort)/Study 3 (All) Safety Pool**.

MEDLEY Season 1: Percentage with events was generally similar between the nirsevimab and palivizumab gps across the age at randomisation subgps in the overall pop'n and preterm and CLD/CHD cohorts. In the overall pop'n, the percentage of subjects with an AESI based on selected MedDRA PTs was higher in the nirsevimab gp than in the palivizumab gp in the >6 mth age subgp, mainly observed in the CLD/CHD cohort. In the ≤3.0 mth age at randomisation subgp, no IP-related AESI based on MedDRA PT, IP-related skin reactions, or NOCDs.

Body Weight - Body Weight <2.5 kg on Season 1 Day 1: These infants received the proposed dose and had the highest nirsevimab exposures based on mg/kg body weight (~20 to 30 mg/kg). Based on the assessment of AEs for nirsevimab vs. placebo in **MELODY [All**

Subjects]/Study 3 Safety Pool), safety profile for infants <2.5 kg on Season 1 Day 1 was consistent with the overall pooled study pop'n and balanced between gps in the type and frequency of AEs. In **MELODY [All Subjects]/Study 3 Safety Pool)**, the percentage of subjects with at least one AE was numerically higher in the nirsevimab gp vs. placebo gp (81.0% and 76.5%, respectively). The percentage of subjects with Grade 3 or higher AEs (nirsevimab 10.2% and placebo 12.7% of subjects) and SAEs (nirsevimab 21.3% and placebo 19.6% of subjects) were both generally balanced between treatment gps with no clinically meaningful imbalance by SOC or PT. In **MEDLEY** RSV Season 1, the percentage with events was generally similar between the nirsevimab and palivizumab gps across all Season 1 weight on Day 1 subgps in the overall pop'n; however, there is limited data in the <2.5 kg on Season 1 Day 1 subgp in **MEDLEY** given the small sample size (N=59 nirsevimab and N=30 palivizumab). In the <2.5 kg on Season 1 Day 1 weight subgp, the percentage with AEs was 66.1% (39/59 subjects) in the nirsevimab gp and 73.3% (22/30 subjects) in the palivizumab gp, and the percentage with SAEs was 20.3% (12/59 subjects) and 10.0% (3/30 subjects), respectively. One death occurred in the <2.5 kg on Season 1 Day 1 subgp in a subject in the nirsevimab gp (PT: bronchiolitis). In the <2.5 kg on Season 1 Day 1 subgp, the percentage of subjects with an AESI based on MedDRA PT in the nirsevimab gp (22.0%) was numerically lower than in the palivizumab gp (33.3%); there were no AESIs, IP-related AESI based on MedDRA PT, IP-related skin reactions, or NOCDs.
Gender: In the **MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool**, the percentage with AEs in the nirsevimab and placebo gps was similar in males (84.5% [1151/1362] and 83.6% [541/647], respectively) and females (83.4% [1007/1208] and 81.5% [519/637], respectively). No meaningful differences in type/frequency of AEs by gender.
Race: For each race gp in the **MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool**, no meaningful differences in type and frequency of AEs between treatment gps. The percentage of subjects with AEs in the nirsevimab and placebo gps was similar in White subjects (76.1% [1097/1441] and 76.2% [564/740], respectively), and Black or African American (93.0% [387/416] and 93.3% [166/178], respectively); no clinically meaningful difference by PT. For the Other races gp, a small numerical difference in the percentage with AEs in the nirsevimab gp vs. placebo gp (94.5% [670/709] and 90.2% [330/366], respectively), but no clinically meaningful differences by PT. The percentage of subjects with SAEs in the nirsevimab and placebo gps was numerically lower in the nirsevimab and placebo gps for White subjects (7.9% [114/1441] and 11.1% [82/740], respectively), Black or African American (8.7% [36/416] and 11.8% [21/178], respectively), and Other Races (6.3% [45/709] and 8.7% [32/366], respectively) categories. There was no meaningful difference between race gps for SAEs.
Gestational Age at Birth: No effect on the safety of nirsevimab.
MEDLEY CLD/CHD Subjects who Received Replacement Dose Following Bypass Surgery in Season 1 and Season 2: In Season 1, 8 (nirsevimab gp) and 7 (palivizumab gp) received a replacement dose in the context of cardiopulmonary bypass surgery. None in the nirsevimab gp had AESIs or skin hypersensitivity reactions reported; none had detectable post-baseline ADA to nirsevimab to 360 days post Season 1 Dose 1. In Season 2, 2 subjects in the NIRS/NIRS gp received a replacement dose in the context of cardiopulmonary bypass surgery. No AESIs or skin hypersensitivity reactions reported; no detectable post-baseline ADA to nirsevimab to at least 150 days post first dose.

8.5.2. Safety related to drug-drug interactions and other interactions (vaccines)

Vaccine Exposure: Based on the small amount of available data in the pooled pop'ns for the percentage of subjects with AEs reported within 7 and 28 days after vaccine administration, no clinically meaningful imbalance observed for any particular PT when vaccines co-administered +/- nirsevimab for any vaccine and each of the 7 vaccine categories evaluated.
MELODY (All Subjects)/Study 3 (Proposed Dose) Safety Pool Exposure: Vaccine exposure was generally comparable in the nirsevimab gp to the placebo gp. On the **same day as dosing**, 0.7% of subjects in the nirsevimab gp and 1.2% of subjects in the placebo gp had any vaccine with a total of 48 doses and 32 doses, respectively. The most frequently reported vaccines were

polyvalent DPT-containing vaccine (+/- other antigens) (13 and 8 doses, respectively), rotavirus vaccine (12 and 9 doses, respectively), pneumococcal vaccines (12 and 7 doses, respectively). **Within 7 days** before or after dosing, 7.4% of subjects in the nirsevimab gp and 8.6% of subjects in the placebo gp had any vaccine with a total of 420 doses and 218 doses, respectively. The most frequently reported vaccines were polyvalent DPT-containing vaccine (+/- other antigens) (125 and 56 doses, respectively), pneumococcal vaccines (103 and 46 doses, respectively), and rotavirus vaccines (100 and 49 doses, respectively). **Within 14 days** before or after dosing, 27.0% of subjects in the nirsevimab gp and 28.9% of subjects in the placebo gp had any vaccine with a total of 1601 and 802 doses, respectively. The most frequently reported vaccines were polyvalent DPT-containing vaccine (+/- other antigens) (489 and 230 doses, respectively), pneumococcal vaccines (426 and 212 doses, respectively), and rotavirus vaccine (417 and 197 doses, respectively).

AE with Vaccine Co-administration

Any Vaccine Co-administration

AEs that occurred **within 7 days after** any co-administered vaccination:

- For subjects who received any vaccine **on the same day as dosing**, the only AEs that occurred were one AE of injection site pain in 1 subject (1/19 [5.3%]) in the nirsevimab gp, and two AEs of rhinitis in 2/16 (12.5%) subjects in the placebo gp;
- For subjects who received any vaccine **within 7 days** before or after dosing, the most frequently reported AEs (> 2 subjects in the nirsevimab gp or placebo gp) in the nirsevimab gp were pyrexia (3/190 [1.6%] subjects) and injection site pain (2/190 [1.1%] subjects) within 7 days after vaccination. No other AEs occurred in >1 subject in the nirsevimab gp and no AEs occurred in >1 subject in the placebo gp;
- For subjects who received any vaccine **within 14 days** before or after dosing, the most frequently reported AEs (>2 nirsevimab or placebo gp) were pyrexia (5/694 [0.7%] subjects and 2/371 [0.5%] subjects, respectively), rhinitis (4/694 [0.6%] subjects and 3/371 [0.8%] subjects, respectively), gastroenteritis (3/694 [0.4%] subjects and 0 subjects, respectively), URTI (3/694 [0.4%] subjects and 0 subjects, respectively), vaccination complication (3/694 [0.4%] subjects and 4/371 [1.1%] subjects, respectively), nasopharyngitis (1/694 [0.1%] subjects and 3/371 [0.8%] subjects, respectively), and nasal congestion (0 subjects and 3/371 [0.8%] subjects, respectively).
- AEs that occurred **within 28 days** after any co-administered vaccination:

- For subjects receiving any vaccine on **the same day** as dosing, the most frequently reported AEs in the nirsevimab gp were infantile colic and URTI (2/19 [10.5%] subjects, each). No other AEs occurred in >1 nirsevimab subject; no AEs occurred in >1 placebo subject;
- For subjects who received any vaccine **within 7 days** before or after dosing, the most frequently reported AEs (≥5 subjects in the nirsevimab gp or placebo gp) were pyrexia (6/190 [3.2%] subjects and 1/110 [0.9%] subjects, respectively), dermatitis diaper (nappy) (5/190 [2.6%] subjects and 1/110 [0.9%] subjects, respectively), infantile colic (5/190 [2.6%] subjects and 0 subjects, respectively), and nasal congestion (5/190 [2.6%] subjects and 5/110 [4.5%] subjects, respectively);
- For subjects who received any vaccine **within 14 days** before or after dosing, the most frequently reported AE (>5 subjects in the nirsevimab gp or placebo gp) was URTI (55/694 [7.9%] subjects and 22/371 [5.9%] subjects, respectively), nasal congestion (27/694 [3.9%] subjects and 12/371 [3.2%] subjects, respectively), nasopharyngitis (24/694 [3.5%] subjects and 17/371 [4.6%] subjects, respectively), dermatitis diaper (nappy) (15/694 [2.2%] subjects and 5/371 [1.3%] subjects, respectively), rhinitis (15/694 [2.2%] subjects and 15/371 [4.0%] subjects, respectively), and pyrexia (13/694 [1.9%] subjects and 3/371 [0.8%] subjects, respectively).

PREGNANCY AND LACTATION: No nirsevimab clinical study has been conducted in pregnant or lactating women as this is not the intended patient pop'n.

Viral resistance: Nirsevimab exhibited activity against both RSV subtype A and B through 150 days post dose for the primary endpoint MA RSV LRTI and the secondary endpoint MA RSV LRTI with hospitalisation **in Study 3, Study 3 (Proposed Dose), MELODY (Primary Cohort), MELODY (Safety Cohort), and the MELODY (Primary Cohort)/Study 3 (Proposed Dose) Pool**, with numerically lower proportions of subjects with primary and secondary events for nirsevimab vs. placebo. In the **MELODY (Primary Cohort),** the majority of cases of MA RSV LRTI (33 of 37 cases overall) were subtype A; in **MELODY (Safety Cohort)** the majority (35 of 41) were subtype B. Since 2015, most amino acid residues in the nirsevimab binding site have remained highly conserved (>99%) at all 25 positions in RSV A and 22 of the 25 positions in RSV B (**Report ID8897-0102, Module 5.3.5.4**). Of the remaining 3 positions in RSV B, one showed >98% sequence conservation and 2 showed >31% sequence conservation due to emergence and prevalence of I206M:Q209R combination of polymorphisms among current circulating strains. Nirsevimab retained neutralisation activity against recombinant RSV-harbouring prevalent F polymorphisms identified in nearly all currently circulating variant strains including those with A103V, L172Q, S173L, K191R, Q209R, and I206M:Q209R in RSV B. Nirsevimab exhibited low level reduced susceptibility against recombinant RSV harbouring I206M (5.0-fold); however, this nirsevimab binding site substitution has been rarely detected in the absence of Q209R since 2015 (0.62%) (**Report ID8897-0102, Module 5.3.5.4**). An additional binding site substitution at S211N which expanded in prevalence in 2022 also retains susceptibility to nirsevimab, both individually (1.2-fold change from ref.) and as co-occurring substitutions (I206M:Q209R: S211N, 0.5-fold change). These results are consistent with the observation that nirsevimab exhibits highly potent and broad antiviral activity against a diverse panel of RSV A and B isolates encoding the most common RSV F sequence variations found among circulating strains (**Report ID8897-0002, ID8897-0011, Module 2.6.2; Report ID8897O-1516, ID8897O-1617, Module 5.3.5.4**). Finally, nirsevimab retained neutralisation activity against recombinant RSV harbouring palivizumab resistance-associated substitutions (K272M and K272T in RSV A and K272N and K272Q in RSV B), indicating a lack of cross-resistance.

8.6. Post marketing experience

None. This drug is only very recently approved in the EU and GB.

8.7. Evaluator's overall conclusions on clinical safety

Across the 5 studies (**Studies 2 and 3, MELODY, MEDLEY and MUSIC**) conducted in the target population, nirsevimab at the single doses administered (50mg or 100mg) IM appears very safe. In the few infants entering their second RSV season in **MEDLEY and MUSIC**, the 200mg IM dose appeared safe. There were no safety concerns in the very and moderately pre-term infants (**Study 2**), preterm infants (<35wGA), infants with chronic heart or lung problems (**MEDLEY**) and immunocompromuised infants (**MUSIC**). Overall, few adverse events are considered to have a
reasonable possibility of having a causal association with nirsevimab. The ADRs based on analysis of 2966 subjects in the nirsevimab gp of the **MELODY (All Subjects)/Study 3 Safety Pool**, as the largest nirsevimab-exposed safety population, has been used to populate the reference safety information in the proposed SmPc for Australia, and the approved EMA and MHRA-approved PI. Considering all pertinent events, the sponsor proposes the adverse drug reaction of rash based on PTs rash, rash maculopapular, and rash macular that occurred within 14 days after administration of nirsevimab in the placebo-controlled studies **MELODY (All Subjects)/Study 3 Safety Pool.** In the **MELODY (All subjects)/Study 3 (Proposed Dose) Safety Pool)** a total of 19 subjects in the nirsevimab gp had at least one event corresponding to these PTs, regardless of the relationship assessment of the investigator, giving a frequency of 19/2570 subjects (≥1/1000 to <1/100, defined as 'uncommon') and a rate of 0.7% in RSV Season 1. As the Clinical Reviewer, I concur with this decision. ADA positivity to nirsevimab was generally low, and when it did occur was not associated with altered nirsevimab PK, or any safety signal. In the small number of subjects who received a second dose on 200mg IM in

Season 2, there was no evidence of priming if they had received nirsevimab in RSV Season 1 or boosting of an anamnestic response based on their Season 1 and Season 2 immunogenicity data.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
1) Nirsevimab is long-acting mAb given IM for prevention of RSV, a single IM dose provides nAb levels in the protective range for the duration of an average RSV season of 5 months. 2) Clinical efficacy (incidence of medically attended RSV LRTI in the outpatient and inpatient setting) has been confirmed in the **MELODY** study which enrolled preterm infants entering their first RSV season. 2) Straightforward weight-based dosing of 50mg in those <5kg and 100mg in those weighing ≥5kg at the time of IM dosing. 3) The nAb levels correlate with nirsevimab levels, demonstrating that this mAb's activity is via RSV neutralisation. 4) No host receptor target, so this mAb is very safe. Its safety was demonstrated in all the studies. Incidence of ADA was very low, and even when it occurred did not impact the PK of nirsevimab or the safety profile. 5) Effective against both RSV subtype A and B, which are the dominant strains. The target is highly conserved and there was no significant emergence of resistance.	1) The **MUSIC** study enrolling immuncompromised children is ongoing. To date, there are too few cases of Medically attended RSV LRTI to confirm clinical benefit. 2) Clinical efficacy could not be confirmed in the **MEDLEY** study, because of low circulating rates of RSV. 3) Relatively few infants in either **MEDLEY** or **MUSIC** have been exposed to the second dose of 200mg IM, while safety looks similar, numbers are not that large, so further data would be important in regard to both safety and efficacy. 4) Clinical efficacy of the second 200mg dose was not demonstrated because of very low circulating rates of RSV. 5) The pivotal studies were all conducted during and impacted by COVID-19. Although mitigation strategies appear to have worked well, it has been more challenging to demonstrate the clinical efficacy of nirsevimab in some of these studies, because of the unusually low levels of circulating RSV 6) Few children (n=8) underwent cardiopulmonary bypass and received a second dose of nirsevimab around this time. However, in the few that did receive this second dose it appeared safe. It makes sense to offer extra protection against RSV at a time when acquisition of RSV could have disasterous consequences.

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
1) Clinical efficacy of the second 200mg dose in the population of infants with CHD, CLD and immuncompromised infants has not been demonstrated largely because of the very low circulating rates of RSV during the conduct of **MEDLEY** and **MUSIC.** 2) Underdosing could occur if weight is not accurately measured. 3) Widespread use of this mAb, could apply selection pressure with emergence of resistance RSV strains.	1) Interim (and not final) analyses from several of the ongoing studies. 2) Limited data on the safety and efficacy in the extremely preterm (GA <29 weeks). 3) Limited experience in infants with HIV, because very few were enrolled in **MUSIC**, however, it is not expected, especially with universal of anti-retroviral therapy, that the efficacy of this mAb should be different in those living with HIV. 4) Dosing in the very small infants with body weight 1 kg to <1.6Kg is based on extrapolation. 3) The COVID-19 pandemic has significantly altered

Risks	Strengths and Uncertainties
	the epidemiology of RSV, and we have seen unusual patterns of RSV as it re-emerges including in the summer months as recently experienced in Australia. For many infants, it is harder to know when/if their first or second RSV Season happened in 2020-2022 because the RSV seasons were so atypical. This may mean we have a significant proportion of older highly vulnerable infants who have never been exposed to RSV and may still benefit from this mAb.

9.3. First round assessment of benefit-risk balance

IM dosing with nirsevimab in the proposed infant population, is highly beneficial with minimal risk. I consider that this long-acting RSV mAb will fill an important therapeutic gap in the prevention of RSV in infants, especially in those with vulnerability to severe disease because of prematurity with/without comorbid conditions.

10. First round recommendation regarding authorisation

I recommend authorisation as requested by the Applicant i.e. That nirsevimab (trade name BEYFORTUS) is indicated for the prevention of RSV lower respiratory tract disease in:
i) Neonates and infants entering or 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, which may include but is not limited to children with: Chronic lung disease of prematurity (CLD); Haemodynamically significant congenital heart disease (CHD); Immunocompromised (IC) states; Down syndrome; Cystic fibrosis (CF); Neuromuscular disease; Congenital airway anomalies.
Infants entering their first RSV season: The recommended dose is a single fixed dose of 50 mg for body weight <5 kg and a single fixed dose of 100 mg for body weight ≥5 kg. BEYFORTUS should be administered from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season.
Children who remain vulnerable to severe RSV disease entering their second RSV season – the recommended dose is a single dose of 200 mg (i.e. 2 x 100 mg intramuscular injections).
For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of BEYFORTUS, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.

11. First round comments on product documentation

11.1. First round comments on draft PI (clinical aspects)

An annotated PI was provided in further documents submitted to the TGA as part of this Application in December 2022. I agree with a single PI which includes both the 50mg and 100mg dose. Section 4.8 on Adverse Effects (Undesirable effects) marries with the EMA and MHRA approved SmPCs. Section 5 on pharmacological properties details the relevant data from pivotal and supportive clinical trials in support of the proposed indication, including the

summary data for the use of the 200mg dose in children with CLD or CHD ≤24 mths of age at higher risk that were enrolled in **MEDLEY**.

11.2. First round comments on draft CMI (clinical aspects)

This CMI is comprehensive, and I have no comments on the clinical aspects.

11.3. First round comments on draft RMP (Summary of Safety Concerns)

Documents provided are the EU-RMP Version, Number 1 Succession 4 07-Sep-2022 and the ASA Vn. Number 1.0 Succession 1 to the European Risk Management Plan for Nirsevimab (Beyfortus™) 28-Sep-2022. In the further documents provided by the Applicant they explained that they would provide the now approved EU RMP (v1s5) but haven't yet as explained in the cover letter. The proposed indication in the EU is for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season, which differs from the proposed indication in Australia, in that the proposed indication in the EU is limited to the first RSV season. However, while all routine Pharmacovigilance (PV) activities outlined in Part III.1 of the EU RMP, are considered relevant to Australia, there do not seem to be any routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, despite the proposed indication for nirsevimab in Australia includes RSV Season 2 dosing in infants with CHD or CLD (+/- cardiac surgery) or who are immunocompromised. What PV activities are being undertaken for those who will receive repeat dosing of nirsevimab? Also, I would like to understand better the following:
- Although routine RSV surveillance is now in place in Australia (since September 2022), what are the thresholds for triggering that the RSV season has begun and that nirsevimab dosing can be initiated?
- How will Pharmacovigilance activities be extended if we start to see unusually long RSV seasons, longer that is, than the traditional RSV season of 5 months, such that breakthrough infections could occur as passive immunity from nirsevimab wanes?
- How is nirsevimab resistance being monitored?

12. Clinical questions

12.1. Clinical questions

12.1.1. Pharmacokinetics

None.

12.1.2. Pharmacodynamics

None.

12.1.3. Efficacy

- I would be interested to know the timelines for the completion of **MEDLEY** and **MUSIC,** including the data on the impact of the increase in RSV that has been seen since public health measures to curtail COVID-19 have ceased almost everywhere in the world.

- Is there any evidence of co-infection with RSV and COVID-19 (especially the highly infectious Omicron subvariants)? What is the clinical impact of co-infection in highly vulnerable infants?

- Is there any evidence of a prolonged RSV season (longer than the usual 5 months) as a rebound effect following the very quiet RSV seasons during COVID-19 related lockdowns etc? If yes, what does this mean for the efficacy of a single dose of nirsevimab?

12.1.4. Safety

None.

12.1.5. PI and CMI

None.

12.2. Additional expert input

None.

13. First round evaluation errata

13.1. Minor editorial changes

None.

13.2. Minor errors of fact

None.

13.3. Significant errors of fact

None.

14. Second round evaluation

The Applicant has provided responses to my clinical questions as listed above in **12.1.3** as follows:

Clinical Reviewer Question: I would be interested to know the timelines for the completion of **MEDLEY** and **MUSIC,** including the data on the impact of the increase in RSV that has been seen since public health measures to curtail COVID-19 have ceased almost everywhere in the world.

Response from Applicant: Datalock for both trials has occurred recently, with the Applicant expecting the final CSRs available in early July 2023.

However, the Applicant did not completely respond to the second part of my question. Is it apparent in the recent datalock, what the impact on both trials has been with the increase in RSV that has been seen since public health measures to curtail COVID-19 have ceased globally?

Clinical Reviewer Question: Is there any evidence of co-infection with RSV and COVID-19 (especially the highly infectious Omicron subvariants)? What is the clinical impact of co-infection in highly vulnerable infants?

Response from Applicant: The Applicant provided a comprehensive response, these data are available in **MELODY**, the overall incidence of co-infection with SARS-CoV-2 (as measured using the Biofire® respiratory 2.1 panel (21 pathogens)) was very low, and none of the co-infected infants required hospitalisation.

Clinical Reviewer Question: Is there any evidence of a prolonged RSV season (longer than the usual 5 months) as a rebound effect following the very quiet RSV seasons during COVID-19 related lockdowns etc? If yes, what does this mean for the efficacy of a single dose of nirsevimab?

Response from Applicant: Whilst atypical RSV seasons were seen in 2021, using Australian surveillance data from 2022, it appears that the RSV season is now back to its usual 5 months duration in the winter months. The Applicant also provided 3 pertinent references.

In addition, the Applicant highlighted an erratum in the Population PK model (which was discussed originally in **Section 19.1.2** of this Clinical report). Erratum documents from February 2023 were provided. The key error was in the derivation of the $AUC_{baselineCL}$ in Season 2. In fact, in the subgroups of special interest in Medley second season i.e. infants with CLD and haemodynamically significant CHD, had even higher levels than initially reported, i.e. 97.7% and 100% respectively. Overall, in MEDLEY second season, $AUC_{baselineCL}$ was 98.4%. Of note the CL in Season 2 appeared to be lower than in Season 1 resulting in these higher observed serum concentrations, but there did not appear to be any safety concerns associated with this, and the explanation for this finding is unclear. Overall, the model did predict nirsevimab concentrations in immunocompromised children, and also the weight-based simulations leading to the conclusion with which I as the Clinical Reviewer agree with i.e. the PopPK model does adequately predict exposure across paediatric subgroups, and that the findings do support the proposed dosing schedule of 50mg for infants <5Kg in bodyweight, and 100mg in those 5Kg or more, in Season 1, and dosing of 200mg in Season 2.

They also highlighted that Beyfortus has now been submitted and approved in Canada (on 19 April 2023). The approved Canadian Monograph was provided in **Module 1.11.2**, and I have reviewed this, and have no comments. In addition, the EU has now submitted a Type II variation to expand the indication to include second season use and this will align with the Australian indication.

15. Second round benefit-risk assessment

15.1. Second round assessment of benefits

The benefits remain unchanged from my recommendations in **Section 9.1**

15.2. Second round assessment of risks

The risks remain unchanged from my recommendations in **Section 9.2**

15.3. Second round assessment of benefit-risk balance

My benefit-risk balance remains unchanged i.e. 'IM dosing with nirsevimab in the proposed infant population, is highly beneficial with minimal risk. I consider that this long-acting RSV mAb will fill an important therapeutic gap in the prevention of RSV in infants, especially in those with vulnerability to severe disease because of prematurity with/without comorbid conditions.'

16. Second round recommendation regarding authorisation

This remains the same as detailed in **Section 10**, i.e.

I recommend authorisation as requested by the Applicant i.e. That nirsevimab (trade name BEYFORTUS) is indicated for the prevention of RSV lower respiratory tract disease in:

i) Neonates and infants entering or 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, which may include but is not limited to children with: Chronic lung disease of prematurity (CLD); Haemodynamically significant congenital heart disease (CHD); Immunocompromised (IC) states; Down syndrome; Cystic fibrosis (CF); Neuromuscular disease; Congenital airway anomalies.

Infants entering their first RSV season: The recommended dose is a single fixed dose of 50 mg for body weight <5 kg and a single fixed dose of 100 mg for body weight ≥5 kg. BEYFORTUS should be administered from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season.

Children who remain vulnerable to severe RSV disease entering their second RSV season – the recommended dose is a single dose of 200 mg (i.e. 2 x 100 mg intramuscular injections).

For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of BEYFORTUS, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.

17. Second round comments on product documentation

17.1. Second round comments on draft PI (clinical aspects)

No PI was provided for the round 2 evaluation, as no changes were requested. However, the Applicant is requested to update the PI with relevant results in text and tabular format arising from completed clinical study reports for the **MEDLEY**, **MUSIC** and **MELODY** trials.

17.2. Second round comments on draft CMI (clinical aspects)

A revised CMI (May 2023) was provided. The key changes were to add some minor wording as requested by the Quality reviewer. I am happy with the proposed changes.

17.3. Second round comments on draft RMP (Summary of Safety Concerns)

As previously advised, BEYFORTUS is now approved in the EU. However, the approved EU-RMP (v1s5) was not provided to the TGA at that time as there were only minor amendments compared to the TGA evaluated draft EU-RMP (v1s4 – Sequence 0000). As the EU-RMP has been revised again due to a recent Type II variation to extend the indications to cover second season use, the new draft EU-RMP (v2s1) was provided within this response package from the Applicant. No ASA was provided. The Applicant provided a response to the Clinical Reviewer's Round 1 questions as follows:

Clinical Reviewer Question: What PV activities are being undertaken for those who will receive repeat dosing of nirsevimab?

Response from Applicant: The Applicant re-emphasised that as the drug has no endogenous host target, the potential for immunogenicity adverse events is low. Reassuringly too in the 180 children in MEDLEY with CLD or CHD who received dosing in season 2 was the same as in season 1, and well tolerated. Hence, routine PV activity will be applied to those receiving second dosing. As the Clinical Reviewer, I am satisfied with this response.

Clinical Reviewer Question: Although routine RSV surveillance is now in place in Australia (since September 2022), what are the thresholds for triggering that the RSV season has begun and that nirsevimab dosing can be initiated?
Clinical Reviewer Question:
How will Pharmacovigilance activities be extended if we start to see unusually long RSV seasons, longer that is, than the traditional RSV season of 5 months, such that breakthrough infections could occur as passive immunity from nirsevimab wanes?

Response from Applicant: This would be down to the countrys themselves and regional health departments within country. The Applicant also added that the adverse event database will also capture lack of efficacy and/or breakthrough infections, both of which might suggest a changing pattern of the RSV season. The Clinical Reviewer accepts this response, but it will need close

surveillance in country and in region to determine when the RSV season does actually start and finish.

Clinical Reviewer Question: How is nirsevimab resistance being monitored?

Response from Applicant: There are ongoing molecular surveillance studies, which includes 1 site in Australia for the INFORM-RSV study. The study periods for the 3 studies are 2015-2024+ for OUTSMART-RSV, 2017-2029+ for INFORM-RSV and 2021-2024+ for SEARCH-RSV. Open-source genomic databases (e.g. NCBI GenBank), spontaneous case reports and publications will also inform on breakthrough infections due to nirsevimab escape variants. Moreover, year 7 data from OUTSMART covering the 2021/2022 season, and year 5 data from INFORM covering 2022 are expected imminently. The Clinical Revewer is happy with this response.

In addition, the Applicant provided further responses raised on the Risk Management Evaluation report. The Clinical Reviewer defers to this reviewer, but broadly speaking, she is happy with these responses. Specifically, she notes that a revised ASA will be provided once the final CSRs for MELODY and MEDLEY are provided, which is imminent (July 2023). This is the reason why a revised ASA has not been provided with this report.

RESPONSE TO QUESTIONS ON THE RISK MANAGEMENT PLAN EVALUATION REPORT
Pharmacovigilance plan
Recommendation 4. The results of the ongoing additional pharmacovigilance studies will be applicable to the Australian population. When available a revised RMP which considers the completed study outcomes should be submitted to the TGA for review.
Response from Applicant: AstraZeneca acknowledges TGA's request for a revised RMP once the ongoing pharmacovigilance studies (**MELODY** and **MEDLEY**) have been finalised. AstraZeneca can confirm that these studies are now complete and the final CSRs for **MELODY** and **MEDLEY** are expected to be available early July just after Milestone 5. Based on preliminary results for **MELODY** and **MEDLEY**, no additional safety concerns have been identified. The CSRs can be provided to TGA as soon as available as part of this Category 1 application during the evaluation period for BEYFORTUS, should TGA be amenable to this strategy.
As a result, these studies can be removed from the EU-RMP missing information. However, this will not occur until after the final CSRs have been provided to the EMA as a standalone variation with a subsequent EU-RMP variation then submitted to remove MELODY and MEDLEY from the missing information. Hence the revised EU-RMP is not expected to be EMA approved until after BEYFORTUS approval in Australia. AstraZeneca therefore proposes to instead remove these as missing information via revision to the ASA only. A revised ASA can be provided once the final CSRs have been submitted to TGA. Consequently, a revised ASA (in line with the provided draft EU-RMP v2s1) has not been provided as part of this response. AstraZeneca hopes that this proposal is acceptable.

Question from the Clinical Reviewer: Can the Applicant clarify that final CSRs are awaited for all three studies i.e. **MEDLEY**, **MUSIC** and **MELODY**? I believe all 3 CSRs are still awaited, in which case please provide the final CSRs for the **MEDLEY**, **MUSIC** and **MELODY** to the TGA as soon as they are available. In addition, the Sponsor is requested the summarise the additional data from these final reports in text and tabular format as part of their Milestone 5 response.

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19. Supporting information, tables and figures

19.1. Clinical pharmacology study synopses

19.1.1. Synopses of PK studies

Table 26. Synopses of PK studies – Study 1 and -2

Study D5290C00001: **A Phase 1, Randomized, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI8897 in Healthy Adults**

The original protocol was dated 04-Feb-2014. Subsequent amendments are detailed in the **CSR Table 9.8.1-1**

Location: Single centre in the USA; **Dates of the study:** Apr 2014 to Jun 2015

Presentation: Griffin MP, et al. A passive vaccine approach to RSV prophylaxis for all infants: results of a phase 1 Study in healthy adult volunteers. ID Week, Oct 7-11, San Diego, CA, and RSV Vaccines for the World, Nov 18-20, La Jolla, California.

Study design and Primary objectives	**Study gps**
Study design: Phase 1, first-time-in-human, randomised, double-blind, placebo-controlled, dose-escalation study **Primary Objective:** Safety & tolerability of MEDI8897 vs. placebo when administered as a single, fixed IV dose of 300, 1000, or 3000 mg, or IM dose of 100 or 300mg to healthy adult subjects. **Secondary Objectives:** PK, and ADA **Exploratory objectives:** 1. To determine endogenous anti-RSV nAb in serum and nasal wash and examine change in levels over time; 2. To demonstrate that MEDI8897 maintains functional activity for at least 6 mths; 3. To determine MEDI8897 conc'ns in nasal wash. **Pop'n (age):** Healthy males/females aged ≥18 to <50 years	**Table 27** summarises the treatment assignment. **Cohort 1** (MEDI8897 300 mg or placebo IV), 2 initial subjects were randomised 1:1 to receive MEDI8897 or placebo, followed for 48 hrs before the remaining subjects in Cohort 1 were randomised (5:1) and dosed. Escalation to the next dose level after the 7-day safety follow-up if no safety concerns were identified at the previous dose level. Subjects in the 1000 and 3000mg IV dose cohorts were randomly assigned in a 3:1 ratio to receive MEDI8897 or placebo. For IM dosing, 8 subjects (100mg cohort) and 104 subjects (300-mg cohort) randomly assigned in a 3:1 ratio to receive MEDI8897 or placebo. IM dosing in the 100-mg dose cohort began after the 7-day safety follow-up in Cohort 1 completed and no safety concerns were identified. Escalation to the 300mg IM dose cohort occurred after the 7-day safety follow-up if no safety concerns were identified at the 100mg IM dose level. A higher nos. of subjects planned in the 300mg IM dose cohort to support IM dosing in infants. All subjects followed for ≈360 days (≈5 half-lives) for safety after dosing. **Study drugs: MEDI8897**: Manufacturer MedImmune. **Content**: 5 mL lyophilized vial with nominal 100 mg of MEDI8897 post reconstitution containing 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.04% (w/v) polysorbate 80, pH 6.0. **Lot nos**: B1400005. **Placebo:** Manufacturer MedImmune**. Content:** 3-mL vial with nominal 1.0-mL solution containing 30 mM histidine/histidine-HCl, 80 mM arginine- HCl, 120 mM sucrose, 0.04% (w/v) polysorbate 80, pH 6.0. **Lot nos**. B1300028 **Table 27. Treatment Assignment in Study 1**

Dose Level (mg) and Route of Administration	Number of Subjects Randomized to IP		Randomization Ratio (MEDI8897:Placebo)
	MEDI8897	Placebo	
300 IV	1	1	1:1
	5	1	5:1
1000 IV	6	2	3:1
3000 IV	6	2	
100 IM	6	2	
300 IM	78	26	

IM = intramuscular; IP = investigational product; IV = intravenous.

Key inclusion criteria: written informed consent; non-pregnant if female and of child-bearing potential 2 methods of contraception; aged 18-49 years inclusive

Methodology/data collection: See also **Table 9.5.1.2-1 Schedule of Study Procedures in the CSR.** Subjects evaluated at screening, days 1 (pre-dosing, dosing, end of dosing, 8 hrs post-dosing), 2, 4, 6, 8, 15, 22, 31, 61, 91, 121, 151, 181, 271, 361 for AEs & concomitant medications. Blood samples and urinalysis for safety drawn at screening, and days 1 (pre-dosing), 6, 15, 31, 91. Blood samples for PK analysis drawn on days 1 (pre-dosing, end of dosing, 8 hrs post-dosing), 2, 4, 6, 8, 15, 22, 31, 61, 91, 121, 151, 181, 271, 361. Samples for ADA analysis pre-dose on day 1, then days 15, 31, 91, 181, 271, 361. Samples for PK nasal wash on day 1 pre-dosing, then days 6, 31, 91, 181. Samples for anti-RSV neutralising Ab in serum on day 1 pre-dose, and 8 hrs post-dosing, then days 6, 31, 61, 181, 361.
Sample size: No formal sample size calculation, 136 subjects were planned to be enrolled.
Safety and tolerability evaluations: Recorded throughout the study. Safety based on incidence & severity of TEAEs, changes in physical exam, vital signs, lab values. MedDRA (vs. 18) coding used. AEs of hepatic function abnormality of special interest to the sponsor were defined as any increase in ALT or AST to >3 × ULN and concurrent increase in bilirubin to >2 × ULN. Other AESI were anaphylaxis, hypersensitivity, Infusion-Related Reactions; Immune Complex Disease; thrombocytopaenia; NOCD. Vital sign measurements obtained on days 1 and 2.
Bioanalytical Methods: PK: MEDI8897 conc'ns in human serum measured by the Clinical Testing Lab at MedImmune (Gaithersburg, Maryland) using a colorimetric ELISA method developed and validated by MedImmune. The validation of method SOP CT-050832 "Quantitative ELISA for the Measurement of MED8897 conc'ns in Human Serum" is described in MedImmune validation report **CTVR-0101**. Calibration standards ranging from 0.13 to 96.0 µg/mL and QC samples at conc'ns of 1.5, 6.0 and 24.0 µg/mL were prepared by adding MEDI8897 reference standard into pooled human serum. The sensitivity of the assay in 100% serum matrix was 0.5 µg/mL and ULOQ was 32.0 µg/mL. The human nasal wash samples tested by the Clinical Testing Lab at MedImmune using a colorimetric ELISA method that was developed and validated by MedImmune. The validation of method SOP CT-050834 "Quantitative ELISA for the Measurement of MEDI8897 conc'ns in Human Nasal Wash" is described in MedImmune validation report **CTVR-0103**. The validated measurement range of the assay was 20.0 ng/mL to 1280.0 ng/mL for 50% nasal wash samples (40.0 ng/mL to 2560.0 ng/mL for 100% nasal wash sample values). Measured sample conc'ns were multiplied by a factor of two to determine the final reported conc'ns in order to account for the 1:2 dilution performed in sample preparation. Evaluations performed by MedImmune used an electrochemiluminescent solution phase bridging immunoassay employing the Meso Scale Discovery platform. The method (SOP CT-050833) was developed and validated by MedImmune as described in validation report **CTVR-0102**. The method employed pooled normal human serum as the negative control and pooled normal human serum spiked with a goat anti-MEDI8897 antibody (surrogate control) at 2 levels above detection (50.0 and 1000 ng/mL) as positive controls. Tiered analyses were performed to include screening, confirmatory, and titre assay components, and the positive-negative cut points were statistically determined from drug-naive validation samples.
ADA: Samples confirmed ADA positive if the percent inhibition of response in the presence of drug was ≥56.4% confirmatory cut point established during validation. Confirmed positive samples were then measured in a titre assay. Titres were performed by serially diluting samples with negative control serum and were reported as the reciprocal of the highest dilution (≥ the 1:50 minimum required sample dilution) that measured positive in the assay, before returning a negative response. Titres for negative samples were reported as <50. The estimated detection limit of the screening assay using the surrogate goat antibody was 22.9 ng/mL and ADA levels of 250 ng/mL were detectable in serum containing 50 µg/mL.
Anti-RSV nAbs: Performed by BioAgilytix using a cell-based RSV neutralisation assay. The serum samples and nasal wash samples were tested for RSV nAb titres using a green fluorescent protein-tagged RSV A2 microneutralisation assay (without complement). The LLOQ for the anti-RSV neutralisation assay was 3.32 (log_2 scale); assay was performed as described (Patton).

Statistical analysis: Primary variables: The planned nos. of subjects considered adequate to assess the primary and secondary objectives.
Safety: TEAEs and TE SAEs summarised by dose level treatment gp and active treatment gp total for MEDI8897, by SOC and PT using MedDRA, by type, incidence, severity and relationship to IP. Specific AEs were counted once for each subject for calculating percentages; in addition, if the same AE occurred multiple times within a particular subject, the highest severity and level of relationship observed was reported. Nontreatment-emergent AEs/SAEs were presented in the listings.

PK: Noncompartmental analysis was conducted using Phoenix 64 WinNolin 6.3 (Pharsight, Mountain View, CA). Single-dose PK parameters were estimated for IV dosing: AUC, C_{max}, t_{max}, $t_{1/2}$, $AUC_{0-\infty}$, V_{ss}, V_z, and CL. Similarly for the IM dosing, AUC, C_{max}, T_{max}, $t_{½}$, CL/F, F, V_{ss}/F, and V_z/F were estimated.
ADA responses: Summarised descriptively as nos. and percentage of subjects who developed anti-MEDI8897 antibodies at each visit by dose level treatment gp and by active treatment gp total. For those with a positive assessment, the ADA titre results were summarised.
Anti-RSV nAb: Serum and nasal wash conc'ns were summarised by GMTs and GMFRs and corresponding 95% CI for each treatment gp at each visit using t-test assuming log normal distribution, and baseline GMT and corresponding 95% CI was also summarised. For anti-RSV neutralisation results reported as lower than the LLOQ, a value equal to half of the LLOQ was imputed in the calculation. The LLOQ for anti-RSV neutralisation (log_2 scale) is 3.32. For example, for anti-RSV neutralisation antibody titre on log_2 scale reported as lower than the LLOQ (<3.32), a value equal to the LLOQ - 1 (value of 2.32) was imputed for the summaries. GMT was calculated as: anti-log_2[mean(log_2xi)], where xi is the assay results (titre) for subject i. GMFR was calculated as: anti-log_2[mean(log_2yi)], where yi is the post dose antibody titre fold rise from baseline for each subject. The proportion of subjects with ≥3-fold rise and ≥4-fold rise in titre from baseline and corresponding 95% Clopper-Pearson exact CI summarised. **Post unblinding changes**: Analysis of anti-RSV antibody conc'ns in serum and nasal wash summarised by GMTs and GMFRs and corresponding 95% CI for each treatment gp at each visit.
Demographics/baseline characteristics; safety data: Summarised and tabulated.

Results: 136 subjects were randomised between 18-Apr and 19-Jun-2014 to MEDI8897 300 mg IV (n = 6); MEDI8897 1000 mg IV (n = 6), MEDI8897 3000 mg IV (n = 6), MEDI8897 100 mg IM (n = 6), MEDI8897 300 mg IM (n = 78) or placebo (n = 34). 125 subjects (91.9%) completed the study through Day 361. Two subjects withdrew consent (one from the MEDI8897 300 mg IM gp and one from the placebo gp), one subject (placebo gp) was terminated due to noncompliance and 8 subjects were lost to follow-up (4 in the MEDI8897 total gp and 4 in the placebo gp). Withdrawal of consent was not related to any AEs.
Demographics: Demographics similar for MEDI8897 and placebo recipients. The mean (SD) age of subjects in the MEDI8897 total gp and placebo gp was 31.0 (7.8) and 29.2 (8.6) yrs, respectively. Female subjects comprised 52.9% of the MEDI8897 gp and 55.9% of the placebo gp. Just over a half of the subjects were Black or African American (54.9% in the MEDI8897 total gp, and 61.8% in the placebo gp). Subjects had a mean (SD) weight of 77.98 (14.87) kg in the MEDI8897 total gp and 80.50 (16.85) kg in the placebo gp.
2 interim analyses were conducted, one at 90 days, the other at 6 mths after dosing. The 90-day interim data were submitted to the FDA on 31-Oct-2014 (Serial Nos 013) in support of the IND application; the 6-mth data were submitted to the FDA on 09-Dec-2014 (Serial Nos. 014) in support of the IND application.
Ninety-day Interim Analysis for PK, ADA and Safety: Linear PK was observed, following increasing doses by either route of administration. Peak conc'ns in IM cohorts were achieved in 5 to 9 days. The estimated $t_{1/2}$ was 85 days with no difference between the IV and IM gps. Bioavailability (F) from IM dosing was estimated to be 78%. The CL and V_z were estimated to be 0.042 L/day and 2.7 L, respectively. The predicted 3- to 4-fold increase in the $t_{1/2}$ of MEDI8897 compared to a standard IgG antibody was confirmed. A total of 6 subjects in the MEDI8897 total (5.9%) and 3 subjects in the placebo (9.1%) gps had ADA detected post-baseline. The highest titre detected was 1:200. At the 90-day interim analysis 50% of subjects in both the MEDI8897 total and placebo gps reported an AE. AEs judged to be related to study drug were reported in 17.6% of MEDI8897 total and 29.4% of placebo recipients. There was one SAE of gunshot wound in a MEDI8897 recipient. AEs with ≥Grade 3 severity were reported in 2 subjects (2%) in the MEDI8897 total gp (one for a face injury and the other for a gunshot wound) and 1 subject (2.9%) in the placebo gp (increased blood creatine phosphokinase (CPK)). The most frequently reported AEs in the MEDI8897 total gp were headache (9 subjects, 8.8%), URTI; 8 subjects, 7.8%, and UTI; 4 subjects, 3.9%). All other AEs occurred in ≤3 subjects. The most frequently reported AEs in the placebo gp were headache (5 subjects, 14.7%) and paraesthesia (2 subjects, 5.9%), and all other AEs occurred in 1 subject.
Six-mth Interim Analysis Results for PK, ADA and Safety: Mean $t_{1/2}$ of MEDI8897 ranged from 69 to 77 days across dose gps, and bioavailability after IM administration was 85%. The mean pop'n CL and V_z were 49.9 mL/day and 2.96 L, respectively. The predicted 3- to 4-fold **i**ncrease in the $t_{1/2}$ of MEDI8897 compared to a standard IgG antibody was again confirmed. ADA was detected in a similar proportion of MEDI8897 total and placebo gps. At 6-mths, three additional subjects in the MEDI8897 total gp had ADA detected. Therefore, a total of 9 subjects (8.8%) in the MEDI8897 total and 3 subjects (9.1%) in the placebo

gps that had ADA detected post-baseline. The highest titre detected was 1:400. The presence and titre of ADA had no effect on PK or the safety profile. The safety profile at the 6-mth interim analysis was similar to that at the 90-day interim analysis. No new SAEs, ≥Grade 3 AEs, or related AEs reported at the 6-mth interim analysis. The most frequently reported AEs in the MEDI8897 total gp were URTI (14 subjects, 13.7%), headache (10 subjects, 9.8%), and UTI (5 subjects, 4.9%). All other AEs occurred in ≤3 subjects. The most frequently reported AEs in the placebo gp were headache (5 subjects, 14.7%), blood CPK increased (2 subjects, 5.9%), and paraesthesia (2 subjects, 5.9%). All other AEs occurred in 1 subject. No AESI, NOCD, deaths at 90-day or 6-mth interim analysis.

Final results. PK in Serum: Peak conc'ns observed immediately post dose in all IV dose gps. Time to peak conc'ns upon administration of IM dose ranged from 5 to 9 days. Overall, mean $t_{1/2}$ of MEDI8897 ranged from 85-117 days across the IV and IM dose gps. PK exposure increased approximately dose proportionally in the IV cohorts. For IV infusion, mean C_{max} increased from 97.0 µg/mL at 300 mg to 1163 µg/mL at 3000 mg (**Table 28).** Mean AUC_{last} increased approximately dose proportionally from 5876 day·µg/mL at 300 mg to 59202 at 3000 mg day·µg/mL. Mean AUC_{∞} also increased approximately dose proportionally from 6715 day·µg/mL at 300 mg to 63580 day·µg/mL at 3000 mg. Mean CL ranged from 40.3 mL/day to 47.6 mL/day across the IV dose gps. Serum $t_{1/2}$ of MEDI8897 for IV dosing was estimated to be 90 -117 days in the IV cohorts.

Table 28. Mean MEDI8897 Serum Single Dose PK Parameters in Study 1

Cohort	t_{max} [day(s)], %CV, n	C_{max} (µg/mL), %CV, n	$AUC_{0\text{-}inf}$ (day*µg/mL), %CV, n	$t_{1/2}$ (days), %CV, n	CL/F*(mL/day), %CV, n	V_z/F†(L), %CV, n
300 mg IV	0.08	97.0	6714.8	117	46.1	7.7
n = 6	172	21.9	21.7	19.6	17.3	24.8
	n = 6	n = 6	n = 5	n = 5	n = 5	n = 5
1000 mg IV	0.06	333.8	25320	92.0	40.3	5.4
n = 6	0	22.4	17	12.6	15.4	26.7
	n = 6	n = 6	n = 5	n = 5	n = 5	n = 5
3000 mg IV	0.21	1163	63580	89.8	47.6	6.1
n = 6	62.7	23.8	10.4	18.2	10.6	18.5
	n = 6	n = 6	n = 5	n = 5	n = 5	n = 5
100 mg IM	5.5	20.4	2249.1	103	45.5	6.8
n = 6	71.4	29.4	17.9	11.3	15.4	24.5
	n = 6	n = 6	n = 5	n = 5	n = 5	n = 5
300 mg IM	9.4	47.5	5193.7	85.3	64.6	7.4
n = 78	78.4	26.2	32.1	30.8	37.7	34
	n = 78	n = 78	n = 75	n = 75	n = 75	n = 75

%CV = percentage coefficient of variation; $AUC_{0\text{-}inf}$ = area under the curve from time 0 to infinity; C_{max} = maximum concentration; CL = clearance; F=bioavailability following IM administration; IM=intramuscular; IV=intravenous; n = number of subjects; PK=pharmacokinetics; $t_{1/2}$ = terminal half-life; t_{max} = time to reach maximum concentration; V_2=volume of distribution;

*CL/F (extravascular) for the IM dose groups.

†V2/F (extravascular) for the IM dose groups

Following 100mg and 300mg single IM dose, peak conc'ns observed on Day 6 and Day 10, respectively. Mean C_{max} increased slightly less than dose proportionally from 20.4 µg/mL at the 100mg dose level to 47.5 µg/mL at the 300mg dose level. Mean AUC_{last} and AUC_{∞} also increased slightly less than dose proportionally from 2052 day·µg/mL and 2249 day·µg/mL at the 100mg dose level to 4761 day·µg/mL and 5194 day·µg/mL at the 300–mg dose level, respectively. Mean

extravascular CL ranged from 45.5 mL/day to 64.6 mL/day. Serum $t_{1/2}$ for IM dosing was estimated to be 85 - 103 days and bioavailability of MEDI8897 in the 300-mg IM cohort in comparison with 300-mg IV cohort was 77.3%. The popPK modelling estimate for CL was 43.2 mL/d in the majority of subjects and the estimate for V_z was 3.2 L. Model-estimated systemic bioavailability following IM administration was 87%.

ADA Responses to MEDI8897: In the MEDI8897 total gp, post-baseline ADA was detected in 14 subjects (14/102, 13.7%), including 13 subjects in the MEDI8897 300 mg IM gp and 1 subject in the MEDI8897 1000 mg IV gp. The highest titre was 1:800. In the placebo gp, post-baseline ADA was detected in 5 subjects (5/33, 15.2%), with the highest titre of 1:400. ADA persistent responses were observed in 6 subjects (6/102, 5.9%) in the MEDI8897 gp (5 in MEDI8897 300 mg IM and 1 in MEDI8897 1000 mg IV) with titres ranging from 1:50 to 1:400 in those subjects. ADA persistent positive responses were detected in 5 subjects (5/33; 15.2%) in the placebo gp also with titres ranging from 1:50 to 1:400. On Day 361, ADA was detected in 5 subjects in the MEDI8897 total (5/95; 5.3%) and 3 subjects in the placebo (3/28; 10.7%) gps. The highest titre at Day 361 was 1:200 for both the MEDI8897 total and placebo gps. Regarding ADA and AEs, in the MEDI8897 total gp, at least one AE was reported in 11 of the 14 subjects (78.6%) in whom ADA was detected, and in 53 of the 88 subjects (60.2%) in whom ADA was not detected. Overall, the types of AEs seen with/without ADA were similar. Of the 14 subjects in the MEDI8897 total gp in whom ADA was detected, 17 AEs were reported in 11 subjects (1 subject in MEDI8897 1000 mg IV gp and 10 in the MEDI8897 300 mg IM gp. These included: one subject with epistaxis, nasal congestion and headache; one subject with dermatitis contact; one subject with musculoskeletal pain and gastroenteritis; one subject with pyrexia and vomiting; one subject with gunshot wound; one subject with tooth abscess; one subject with abdominal pain and dizziness; one subject with conjunctivitis viral; one subject with URTI; one subject with URTI and acarodermatitis; and one subject with blood bilirubin increased and arthralgia. The presence and titre of ADA had no effect on the PK or safety profile.

Serum Anti-RSV nAbs: Detected in both the placebo subjects and the MEDI8897 subjects **prior** to administration of MEDI8897 or placebo. Baseline RSV nAbs were similar in all gps with GMTs of 296.60, 335.85, 445.21, 410.15, 175.87 and 389.65 for the placebo, 300mg IV, 1,000mg IV, 3000mg IV, 100mg IM and 300 mg IM gps, respectively. At the subject level, baseline RSV nAbs were heterogeneous within and across gps with titres ranging from 5.06 to 11.69 log2 IC_{50} titre. nAbs in the placebo gp were stable over the course of the year-long study with GMTs ranging from a low of 284.57 to a high of 388.12 at Day 361 (GMFR =1.22 from baseline). Based on a 4-fold rise in nAb titres, one subject in the placebo gp may have had an RSV infection or exposure. RSV nAb titres increased following administration of MEDI8897 in a dose-dependent manner with the highest titres in the IV gps being detected at the 8 hrs post-infusion and the highest titres being detected at Day 6 for the two IM gps. The GMFRs for the placebo, 300mg IV, 1,000mg IV and 3,000mg IV MEDI8897 gps were 0.96, 27.41, 33.75 and 96.00, respectively, at 8 hrs post-infusion. The GMFRs at Day 6 for the placebo, 100mg IM and 300mg IM were 1.05, 13.63 and 12.46, respectively. The highest level of RSV nAbs were detected at the end of infusion in the MEDI8897 3,000 mg IV gp with a titre of 39,375.21. At Day 31, following administration of MEDI8897, 5 subjects (5/6; 83.3%) in the MEDI8897 100 mg IM gp, and 70 subjects (70/77; 90.9%) in the MEDI8897 300 mg IM gp had ≥4-fold rise in nAbs compared to baseline. Similarly, at Day 31, 100% of subjects in the MEDI8897 300 mg IV, MEDI8897 1000 mg IV and the MEDI8897 3000 mg IV gps, had a ≥4-fold rise in neutralising antibody titres compared to baseline. None of the subjects in placebo gp had a ≥4-fold rise in nAbs compared to baseline on Day 31. At Day 181, RSV nAb titres for all MEDI8897 gps were higher than placebo. RSV nAb titres for the 300mg IV and IM MEDI8897 gps were similar at each visit from Day 6 through Day 361. In general, RSV nAb titres were dose dependent and were comparable to and correlated with serum MEDI8897 conc'ns, confirming MEDI8897 ex vivo anti-RSV neutralising activity.

Nasal Wash Anti-RSV Neutralising Antibodies: At baseline, 4 of the 136 subjects were positive for RSV nasal antibodies and the levels were low with titres of 3.70, 3.75, 5.26, and 6.43 $\log_2$ IC_{50}. Following administration of MEDI8897, 3 subjects had detectable nAbs in nasal wash at Day 6 and these titres were also low with values of 4.06, 3.89 and 3.70. A fourth subject had detectable levels of nasal wash RSV nAbs at Day 181 with a titre of 4.47.

Nasal Wash MEDI8897 conc'ns: MEDI8897 was detected in nasal wash in 3 subjects on Day 6 across all cohorts. MEDI8897 nasal conc'ns on Day 6 were 44.89 and 85.63 ng/mL in 2 subjects in the 3000mg IV gp and 40.96 ng/mL **i**n a subject in the 300mg IM gp. The ratios of nasal wash conc'n to serum conc'n on Day 6 were 0.00007 and 0.00011 for the subjects in the 3000mg IV gp and 0.001 for the subject who received 300mg IM.

Safety summary: No deaths; No AESIs; SAEs of gunshot wound, and appendicitis were reported in 2 out of 78 (2.6%) subjects in the MEDI8897 300 mg IM gp. No subjects permanently discontinued IP due to an AE in this study. Post-baseline vital signs, physical findings and other observations related to safety showed no meaningful changes from baseline to Day 361 for any of the gps. **TEAEs:** The most frequent TEAEs in the MEDI8897 total gp included URTI (19/102; 18.6%), headache (9/102; 8.8%), UTI (6/102, 5.9%), dermatitis contact (5/102; 4.9%), musculoskeletal pain (5/102; 4.9%), nausea (5/102, 4.9%) and vomiting (5/102, 4.9%). The most frequent TEAEs in the placebo gp were headache (6/34; 17.6%), URTI (3/34, 8.8%), nausea (2/34; 5.9%), increased blood CPK level (2/34; 5.9%) and paraesthesia (2/34; 5.9%). **IP-Related TEAE:** 18 subjects in the MEDI8897 gp (17.6%) and 10 subjects in the placebo gp (29.4%) had at least one AE considered by the site investigator as IP-related. IP-related TEAEs with the highest frequency were in the SOC of nervous system disorders [6 (5.9%) MEDI8897; 6 (17.6%) placebo]. All related events were considered Grade 1 for subjects receiving MEDI8897, and Grade 1 or Grade 2 for subjects receiving placebo. There were two Grade 3 TEAEs of highest severity, one in the MEDI8897 300mg IM gp (eye injury) and the other in the placebo gp (increased blood CPK). One TESAE event of Grade 4 highest severity (gunshot wound) was reported in the MEDI8897 300 mg IV, and another of Grade 2 of highest severity (appendicitis) was reported in a MEDI8897 300mg IM. No hypersensitivity reactions.
Evaluator's comments on study design/findings: This is a large Phase 1, first in human study. It enrolled adults, as this was felt the safest approach, even though infants are ultimately the target pop'n. In summary this study showed that in healthy adults the safety profile of MEDI8897 (given IV or IM, and at all the doses explored in this study) was favourable, with a similar proportion of AEs reported in MEDI8897 and placebo recipients. In terms of MEDI8897 PK the mean $t_{1/2}$ ranged from 85 to 117 days, a 3- to 4-fold increase over a standard IgG1 antibody, the time to peak conc'n with IM dosing ranged from 5 to 9 days. The model-estimated systemic bioavailability following IM administration was 87%. Serum anti-RSV nAb titres increased following MEDI8897 administration and were higher than baseline levels in all gps through 180 days post. The incidence of ADA was low, and similar in MEDI8897 and placebo gps; ADA had no effect on PK or safety. The data derived support IM dosing in infants and were explored in **Study D5290C00002** (**Study 2** below).
Study D5290C00002 (Study 2) A Phase 1b/2a Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI8897, a Monoclonal Antibody with an Extended Half-Life Against Respiratory Syncytial Virus, in Healthy Preterm Infants The original protocol was dated was dated 26-Aug-2014.Subsequent amendments detailed in the **CSR Table 9.8.1-1** **Location:** Ten sites in the USA, Chile, and South Africa; **Dates of the study:** Jan2015 to Sep2016

Study design and Primary objectives	**Study gps**
Study design: Phase 1b/2a, randomised, double-blind, placebo*-controlled study **Primary Objective:** To evaluate the safety and tolerability of MEDI8897 compared to placebo when administered as a single fixed IM dose of 10, 25, or 50mg to healthy preterm infants born between 32 wks 0 days and 34 wks 6 days gestational age. **Secondary Objectives to evaluate:** • single-dose serum conc'ns of MEDI8897	Based on the popPK model a single 50-mg fixed IM dose of MEDI8897 was predicted to be the dose that would provide complete protection for infants entering their first RSV season. The weight of infants in this study was expected to range from 2 to 9 kg and predicted serum exposure in this weight range following a single 50-mg fixed IM dose of MEDI8897 was expected to range from 10640 to 3970 µg•day/mL. Predicted serum exposures from IV administration (3000 mg) of MEDI8897 to healthy adults were expected to cover serum exposures for the 50-mg IM dose in infants. Following the highest dose of 3000mg IV in healthy adults, the serum AUC was expected to be 5.4- to 14.5-fold higher and C_{max} was expected to be 8.5- to 31.4-fold higher compared to the predicted exposures from an expected efficacious dose of 50mg IM in a 2-9 kg infant. Three sequential dose-escalation cohorts of 10 subjects each were planned, with 4:1 randomisation (MEDI8897 to placebo) per cohort, at dose levels of 10, 25, and 50 mg MEDI8897. Each subject received a single dose of MEDI8897. Escalation from one dose cohort to the next was dependent on an acceptable safety profile during the first 14 days following dosing in the preceding dose cohort as determined by the Dose Escalation Committee (DEC) review.

• ADA responses to MEDI8897 in serum

Exploratory Objectives:

• To begin collection and evaluation of efficacy data for protection from MA RSV LRTI

• To determine anti-RSV nAb levels in serum

*The pop'n of healthy preterm infants born between 32 wks 0 days and 34 wks 6 days gestational age and who did not meet AAP criteria to receive prophylactic palivizumab treatment was selected after feedback from the US FDA. The US FDA recommended this healthy preterm pop'n based on its higher risk of serious RSV disease than that of older gestational age infants and the proven benefit shown in previous studies of RSV prophylaxis.

Pop'n: Healthy preterm infants born between 32 wks 0 days and 34 wks 6 days gestational age who entered their first RSV season.

Following escalation to, and completion of, the 25-mg escalation cohort, and determination by the DEC that this dose level had an acceptable safety profile, a 25-mg expansion cohort of 30 subjects was enrolled (4:1 MEDI8897 to placebo) in parallel with the 50-mg escalation cohort of 10 subjects. Similarly, following completion of the 50-mg escalation cohort and review of data and determination by the DEC that the safety profile was acceptable, a 50-mg expansion cohort of 30 subjects was enrolled (4:1 MEDI8897 to placebo). Subjects were followed for ≈360 days after dosing for safety, PK, and ADA assessments.

Test Product Dose, Mode of Administration, and Batch Nos:

IP: MEDI8897. **Dose and Form**: 5 mL lyophilized vial with nominal 100 mg of MEDI8897 post reconstitution containing 30 mM histidine/histidine-HCl, 80 mM arginine-HCl, 120 mM sucrose, 0.04% (w/v) polysorbate 80, pH 6.0. **Administration**: IM injection. **Batch/Lot Nos**: B1400005.

Reference Therapy, Dose, Mode of Administration, and Batch Nos:

Reference Therapy: Placebo. **Dose and Form**: Placebo (0.9% saline for injection). **Administration**: IM.

Batch/Lot Nos: Placebo (supplied by sites and recorded at sites)

Table 29. Treatment Assignments in Study 2

Cohort/MEDI8897 Dose Level and Route of Administration	Number of Subjects (Ratio [MEDI8897: placebo])	Treatment Group
Fixed dose escalation		
10 mg IM	10 (4:1)	MEDI8897 (n = 8) or placebo (n = 2)
25 mg IM	10 (4:1)	MEDI8897 (n = 8) or placebo (n = 2)
50 mg IM	10 (4:1)	MEDI8897 (n = 8) or placebo (n = 2)
Fixed dose expansion		
25 mg IM	30 (4:1)	MEDI8897 (n = 24) or placebo (n = 6)
50 mg IM	30 (4:1)	MEDI8897 (n = 24) or placebo (n = 6)

IM = intramuscular

IWRS was used for randomisation to a treatment gp and assignment of blinded investigational product kit nos.

Key inclusion criteria: Healthy preterm infants born between 32 wks 0 days and 34 wks 6 days gestational age who entered their first RSV season at the time of screening; written informed consent by parent/guardian/LAR

Methodology/data collection: Sample size: n=90. Described in detail in **Table 9.5.1.1-1 Study Objectives and Variables Report of the CSR.**

Schedule of Study Procedures in the CSR. Subjects evaluated at screening, days 1 (pre-dosing, dosing, 30 mins post-dose, 1, 2, 3, and 4 hrs post-dose), days 8, 31, 91, 151, 271, 361 for AE/SAEs/AESIs and concomitant medications. Blood samples for safety analyses at screening, and days 8, 31, 151. Blood samples for PK analysis at screening and days, 8, 31, 151, 361. Samples for ADA at screening and days 31, 151, 361. Samples for anti-RSV nAb at screening, days 8, 151, 361.

Criteria for Evaluation: The **primary endpoint** to support the primary objective was the safety and tolerability of MEDI8897 as assessed by the occurrence of all TEAEs, SAEs, AESIs), and clinical lab assessments (i.e. haematology and serum chemistry).

Secondary endpoints: Single-dose MEDI8897 serum conc'ns; incidence of MEDI8897 ADA in serum; Exploratory: Incidence of MA RSV LRTI (inpatient and outpatient) during 5 mths of the RSV season; Serum conc'n of anti-RSV nAb.

Bioanalysis methods: A RT-PCR assay for the detection of RSV was conducted using the FDA-cleared and CE-marked in vitro diagnostic Quidel® Molecular RSV + hMPV assay (510[k] Number: K122189). This was a multiplex RT-PCR assay for the detection and identification of RSV and hMPV ribonucleic acid extracted

from respiratory samples of patients with signs of LRTI. Sanger sequencing and analysis of the RSV G gene used to determine RSV subtype. The RSV G sequencing test was developed and validated by Viracor-IBT Laboratories (Lee's Summit, MO) to identify the sequence of the RSV G gene hypervariable region in respiratory samples of RSV-positive patients.

RSV F Sequencing: Nasal swab specimens positive in the Quidel® Molecular RSV + hMPV assay reflexed for RSV F gene sequencing using a Sanger sequencing assay developed, validated and performed by Viracor-IBT Laboratories (see **Appendix 16.1.13, Validation Report 2112.2847**). Sanger sequencing and analysis of the RSV G gene was performed to determine RSV subtype. The RSV G sequencing test was developed and validated by Viracor-IBT Laboratories (Lee's Summit, MO) to identify the sequence of the RSV G gene hypervariable region in respiratory samples of RSV-positive patients.

ADA: Two assay methods were used. The original method (**Validation Report CTVR-0102, Appendix 16.1.13**) was found to have a high level of positive classifications in a drug-naive pop'n. Prior to the second interim analysis, the analytical method was re-developed to reduce the level of false-positive classifications without compromising assay sensitivity and drug tolerance (**Validation Report CTVR-0147, Appendix 16.1.13**). This improved assay was used for evaluation of samples for the second interim analysis (Day 151) and final analysis (Day 361), and baseline and Day 31 samples were also re-analysed using this newer assay. ADA data from both assays are included but overall study conclusions were based on data from the re-developed assay.

Re-developed ADA Assay Using High-bind Plates: ECL assay developed by MedImmune was also formatted as a solution-phase bridging immunoassay that employed MSD technology for the detection, confirmation, and titration of MEDI8897 ADA in human serum. ADA bound to both biotinylated and ruthenylated forms of MEDI8897 were captured on high-bind streptavidin-coated MSD plates for generation of an ECL signal; all other assay methodology remained unchanged from the standard ADA assay, and both assay methods were shown to have similar sensitivities and drug tolerances. In the screening assay, samples with signal to background responses at or above 1.23 (the screening cut point established during assay validation) were considered potentially positive for the presence of ADA to MEDI8897 and re-tested in the confirmatory assay in the presence and absence of excess MEDI8897. Samples were confirmed ADA positive if the percent inhibition of response in the presence of excess drug was ≥34.1%, the confirmatory cut point established during validation. Titres for negative samples were reported as <50. The estimated detection limit of the screening assay using the surrogate goat anti-MEDI8897 antibody was 16.87 ng/mL, and 125 ng/mL of the surrogate antibody was detectable in serum containing 10 µg/mL MEDI8897.

Evaluation of ADA to MEDI8897 for Presence of Anti-YTE Reactivity: Samples confirmed to contain ADA against MEDI8897 were evaluated for the presence of ADA specifically targeting the YTE domain using a homogeneous bridging assay that employs MSD technology. The analytical method was developed and validated by MedImmune (Validation Report **CIBVR-0006, Appendix 16.1.13**). Positive samples were treated with excess of a control IgG1 antibody with the YTE domain. Samples were considered positive for the presence of ADA targeting the YTE domain if the percent inhibition of response in the presence of excess YTE control antibody was ≥21.22%, the specificity cut point established during validation. The estimated detection limit of the specificity assay using a surrogate mouse monoclonal anti-YTE antibody was 20.84 ng/mL.

Serum Anti-RSV nAb: Performed by BioAgilytix Labs using a cell-based RSV neutralisation assay. Methodology as used in **Study 1** (see above).

Safety: Severity graded using NCI CTCAE vn. 4.03 where applicable for paediatric assessments, with the exception of lab values. Lab values were assessed and reported as AEs by the site investigators if judged to be clinically significant. Determination of severity for AEs not listed in NCI CTCAE was made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as described in the protocol.

Statistical Methods: Tabular summaries presented by treatment gp; listings sorted by treatment gp and subject nos. Placebo gps were pooled together across all cohorts for analyses and presentation of results. Similarly, the original cohort and expansion cohort were combined for analysis of the MEDI8897 25-mg and 50-mg gps, respectively. Categorical data were summarised by the nos. and percentage of subjects in each category. Continuous variables were summarised by descriptive statistics. Additional details of statistical analyses are described in the SAP for the study.

Primary Endpoint: AE, SAEs, AESIs, NOCDs, and MA-LRTIs, summarised by treatment gp and active treatment gp. AE summaries included the type, incidence, seriousness, severity, and relationship to study product. Lab parameters were summarised at each visit by treatment gp and active treatment gp total

for MEDI8897. Frequencies of worst observed Grade 3 to 4 toxicity (using Pediatric Toxicity Tables - AIDS Clinical Trial Group), were presented for each lab parameter by treatment gp and active treatment gp total for MEDI8897. Also, lab parameters were assessed by presenting tables containing information related to 2-grade (or greater) lab shifts from baseline. No statistical hypothesis testing was planned for the safety endpoints. **Secondary Endpoints:** Non-compartmental PK analysis. Actual sample collection times used for the PK parameter estimation. Nominal times used for calculation of summary statistics and mean plots. PK parameters summarised by treatment gp. Serum conc'ns of MEDI8897 presented by subject by time point in the listings. The nos. and percentage of subjects who developed anti-MEDI8897 antibodies were summarised at each visit by treatment gp and active treatment gp total for MEDI8897. For those with a positive assessment, the ADA titre results were summarised. The nos. and percentage of subjects positive for ADA at baseline and positive at any post-baseline time point were also summarised. For those with a positive post-baseline assessment, the percentage who were persistent positive and transient positive were also presented. AEs were summarised by SOC and PT based on MedDRA vn. 19 for subjects with MEDI8897 ADA at any time post-baseline. The effect of MEDI8897 ADA on PK was evaluated by visual examination of PK profiles. **Exploratory Endpoints:** The incidence of RSV MA LRTI from Day 1 through Day 151 was the exploratory efficacy endpoint. The efficacy endpoint was assessed based on RSV test results. An additional analysis for the incidence of all-cause MA LRTI from Day 1 through Day 151 was performed. Analysis of anti-RSV nAb conc'ns in serum was summarised by GMTs and GMFRs and corresponding 95% CI for each treatment gp at each visit using t-test assuming log-normal distribution, and baseline GMT and corresponding 95% CI were summarised. The relationship between MEDI8897 PK and anti-RSV nAb in serum was evaluated using a parametric correlation analysis. Two interim analyses planned to evaluate MEDI8897 serum conc'ns, ADA levels, and safety to support the initiation of a Phase 2b study. These analyses were done 30 days and 6 mths after the last subject was dosed
Results: 89 subjects were dosed and analysed for PK, efficacy, and safety. **Demographics:** Mean (SD) ages in the MEDI8897 total and placebo gps were 6.50 (2.64) and 6.95 (2.63) mths, respectively. Mean gestational age in both the MEDI8897 total and placebo gps was 33.1 wks, and the weight of infants ranged from 1.90 kg to 10.30 kg across all dose gps. Across all dose gps, ≈60% (59.2% of the MEDI8897 total gp; 61.1% of the placebo gp) were female, 57% (57.7% in the MEDI8897 total gp; 55.6% in the placebo gp were Black or African American) were Black or African American. The age ranged from 0.6 mths to 11 mths across all dose gps. The mean (SD) weights on Day 1 in the MEDI8897 total and placebo gps were 6.82 (1.90) kg and 7.31 (1.84) kg, respectively. **Safety:** 66 subjects (93.0%) who received MEDI8897 and 17 subjects (94.4%) who received placebo had ≥1 TEAE. No deaths, AESIs, or NOCDs in any dose gp. Thirteen subjects (18.3%) in the MEDI8897 total gp and 3 subjects (16.7%) in the placebo gp had a MA LRTI. Five subjects (7.0%) who received MEDI8897 had a TEAE assessed by the investigator as related to the IP (2/31 in the MEDI8897 25-mg gp and 3/32 in the MEDI8897 50-mg gp); none of these TEAEs were serious. Three subjects (4.2%) who received MEDI8897 had a TESAE (1/31 in the MEDI8897 25-mg gp and 2/32 in the MEDI8897 50-mg gp); 2 of the 5 TESAEs were ≥Grade 3 (severe) (1 each in the MEDI8897 25-mg and MEDI8897 50-mg dose gps). TEAE were most frequently reported in the SOC of Infections and Infestations (88.7% MEDI8897 total; 94.4% placebo). The most frequently reported TEAEs (≥20%) by PT in the MEDI8897 total gp were URTI (69.0%), gastroenteritis (29.6%), cough (25.4%), pyrexia (22.5%), and otitis media (21.1%). There were no trends by dose of MEDI8897 for these TEAEs. The most frequently reported TEAEs (≥ 20%) by PT in the placebo gp were URTI (66.7%), anaemia (33.3%), gastroenteritis (22.2%), cough (22.2%), and otitis media (22.2%). The pattern of TEAEs was similar for subjects who received placebo or MEDI8897 and did or did not have ADA detected. The ADA results at Day 361 showing an increase in the incidence of ADA in MEDI8897 recipients compared to Day 151, additional ad hoc analyses were conducted to evaluate LRTIs and skin events in subjects who received placebo in comparison to ADA-positive and ADA-negative subjects who received MEDI8897. For these analyses, LRTIs included the PTs of bronchiolitis, bronchitis, LRTI, LRTI viral, and pneumonia. Skin events included the PTs of dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, dermatitis diaper (nappy), dry skin, eczema, rash, and rash papular. In general, there were more LRTI events in MEDI8897 subjects who were ADA-positive than in MEDI8897 subjects who were ADA-negative. Overall, and within 150 days after dosing, there was an increase in the rate of skin events in MEDI8897 subjects who were ADA-positive (vs. ADA-negative). This difference was not observed after Day 151.

All of the skin events were non-specific. There were no events that were consistent with a hypersensitivity event, such as urticaria, generalised rash, or angioedema. All skin events were Grade 1 or 2 in severity, and none were assessed by the investigator as related to study drug. The majority of subjects had a Grade 1 TEAE (MEDI8897 total: 42/71 [59.2%]; placebo: 9/18 [50.0%]). Twenty-two subjects in the MEDI8897 total gp (31.0%) and 8 subjects in the placebo gp (44.4%) had a Grade 2 TEAE. Two subjects (2.8%) who received MEDI8897 had a ≥Grade 3 TEAE i.e. Subject 20007980122, a 6.4-mth-old Black female who received MEDI8897 50 mg, had a Grade 3 TESAE of febrile convulsion; Subject 20007980107, a 5.7-mth-old Black female who received MEDI8897 25 mg, had a Grade 3 TESAE of LRTI.

AE by Causality: The majority of TEAEs across all dose gps were judged by the investigator as not related to IP. 5 subjects (7.0%) who received MEDI8897 had TEAEs considered related to study drug. No TEAEs judged by the investigator to be related to study drug in placebo gp subjects. The only drug-related TEAE reported for more than 1 subject was nasal congestion (1 subject in the MEDI8897 25-mg gp and 1 subject in the MEDI8897 50-mg gp). Additional TEAEs considered to be related to IP (1 subject each) were pyrexia, gastroenteritis, URTI, and wheezing in subjects who received MEDI8897. All were Grade 1. There were no TESAEs, AESIs or NOCDs considered by the investigator to be IP-related.

AESI: No AESIs were reported in this study. **NOCD:** No NOCDs were reported in this study. **Deaths:** No treatment-emergent or nontreatment-emergent deaths. Three subjects who received MEDI8897 had at least 1 TESAE (4.2%); the TESAEs led to inpatient hospitalisation and included LRTI and febrile convulsions. None of these events were considered related to study drug by the investigator. No subjects in the placebo gp had a TESAE.

Vital signs and safety labs: No clinically meaningful changes in vital signs and no clinically significant lab findings for haematology or serum chemistry.

PK (Table 30): After a single IM injection on Day 1, peak conc'ns observed 7 days postdose in all dose gps. Exposure increase was less than dose proportional from 10 to 25 mg MEDI8897 IM doses. However, exposures increased in an approximately dose-proportional manner from 25 to 50 mg MEDI8897 IM doses. Following a single IM dose of 10, 25, or 50 mg in healthy preterm infants, the estimated half-life ranged from 62.5 to 72.9 days. On Day 151, 87% of the MEDI8897 serum conc'ns following the 50 mg IM dose were above the EC_{90} threshold of 6.8 μg/mL.

ADA: ADA detected at any time post-baseline in 28.2% of MEDI8897 recipients and at Day 361 in 26.5% of subjects with available samples. This was a change from Day 151 when no subjects had ADA detected. The reason for this change at Day 361 is not known. No safety findings associated with ADA-positivity. There was a slight increase in the rate of subjects with LRTI, and an increase in the rate of subjects with non-specific skin events overall and within the first 150 days after dosing. This increase in skin events was not observed in the period beyond 150 days after dosing.

Exploratory: To evaluate the efficacy data for protection from RSV MA LRTI. One subject in the MEDI8897 10-mg gp had an event that met the objective clinical criteria for a MA LRTI that was positive for RSV within 150 days after dosing. An additional subject in the MEDI8897 10-mg gp also tested positive for RSV within 150 days after dosing; this subject required medical attention for respiratory illness, but the event did not meet the objective clinical criteria for MA LRTI. No placebo subjects, MEDI8897 25-mg, or MEDI8897 50-mg gps had a RSV MA LRTI reported within 150 days after dosing. Six tested positive for a RSV MA LRTI after Day 151; these subjects were equally distributed across the placebo, MEDI8897 25-mg, and MEDI8897 50-mg gps.

Anti-RSV nAbs: Titres increased following MEDI8897 administration. This increase was dose dependent with ≥95% of subjects in each MEDI8897 dose gp having a ≥4-fold rise from baseline. In the placebo subjects at Day 151, none of the subjects had a ≥3-fold rise from baseline, while in the MEDI8897 gps, 89.4% of the MEDI8897 total gp had a ≥3-fold rise from baseline. Interestingly, at Day 361 in the placebo gp, 80% of infants had a ≥3-fold rise from baseline indicating RSV exposure and seroconversion. Also of note, at Day 361 in the MEDI8897 gps, only 58.1% of infants had a ≥3-fold rise from baseline. While the assumption is that the MEDI8897 subjects would have had the same exposure, it is not known why those subjects did not have a corresponding increase in anti-RSV nAbs.

Table 30. MEDI8897 PK Parameters by Dose in Study 2 (Mean, %CV)

MEDI8897 Dose	T_{max} (day)	C_{max} (µg/mL)	AUC_{1-151} (day*µg/mL)	AUC_{∞} (day*µg/mL)	$t_{½}$ (day)	CL/F (mL/day)	Vz/F (mL)
10 mg IM (n=8)	7.04 0.969 N=5	23.2 40.0 N=5	1940 41.7 N=5	2450 N=1	72.9 N=1	4.08 N=1	429 N=1
25 mg IM (n=31)	7.04 5.60 N=29	30.9 33.8 N=29	2260 39 N=29	4320 24.8 N=6	66.2 11.8 N=6	6.05 21.7 N=6	581 27.4 N=6
50 mg IM (n=32)	6.93 7.91 N=31	71.7 22.1 N=31	5470 26.4 N=31	7510 25.0 N=14	62.5 15.0 N=14	7.01 22.4 N=14	633 26.6 N=14

T_{max} = time at which C_{max} is observed; C_{max} = maximal observed concentration; AUC_{1-151} = area under the concentration-time curve over the interval of day 1 to day 151; AUC_{∞} = area under the curve from time zero to infinity; $t_{1/2}$ = terminal elimination half- life; CL/F = extravascular clearance after IM administration; V_z/F = extravascular volume of distribution after IM administration; N=number of subjects

Safety summary: Similar percentages had at least one AE observed in placebo (94.4%) vs. the MEDI8897 total gp (93.0%). Frequency, type, severity, and pattern of TEAEs are consistent are as expected in this healthy preterm infant pop'n. No safety signals observed with ascending MEDI8897 doses. ADA was detected at any time post-baseline in 28.2% of MEDI8897 recipients and at Day 361 in 26.5%. This was a change from Day 151 when no subjects had ADA detected. No safety findings associated with ADA-positivity. There was an increase in LRTI and skin events noted in the ADA-positives, but no skin events were consistent with hypersensitivity. No deaths, AESI (including hypersensitivity), or NOCDs.

Evaluator's comments on study design/findings: The primary objective of **Study 2** was evaluation of safety and tolerability of MEDI8897 vs. placebo in healthy pre-term infants. No safety signals observed with ascending dose levels or the highest dose of 50 mg IM. MEDI8897 serum $t_{1/2}$ was estimated to be 62.5 to 72.9 days, confirming the extended half-life needed to cover a typical 5 mth RSV season. On Day 151, 87% of the MEDI8897 conc'ns (post 50-mg IM) were >EC_{90} threshold of 6.8 µg/mL. Serum MEDI8897 conc'ns correlated with serum anti-RSV nAbs across all the dose levels, confirming anti-RSV activity of MEDI8897. ADA was detected post-baseline in 28.2% of MEDI8897 recipients and at Day 361 in 26.5% of subjects with available samples. This was a change from Day 151 when no subjects had ADA detected. The incidence of detected ADA was higher at Day 361 than at Day 151, and this seems hard to explain. ADA did not impact the PK at Day 151 and was not associated with any safety signal. The protective efficacy from RSV MA LRTI could not be established as there was only one subject in the MEDI889710-mg gp who met the criteria. No subjects in the placebo, MEDI8897 25-mg, or MEDI8897 50-mg gps had RSV MA LRTI reported within 150 days after dosing; 6 subjects tested positive for a RSV MA LRTI after Day 151; and were equally distributed across placebo, MEDI8897 25-mg, and MEDI8897 50-mg gps. MEDI8897 was associated with dose dependent increases in serum anti-RSV nABs, as expected with ≥95% of subjects in each MEDI8897 dose gp having a ≥4-fold rise from baseline. In the placebo subjects at Day 151, none had a ≥3-fold rise from baseline, while in the MEDI8897 gps, 89.4% of the MEDI8897 total gp had a ≥3-fold rise from baseline. Interestingly, at Day 361 in the placebo gp, 80% of infants had a ≥3-fold rise from baseline indicating RSV-related seroconversion. However, at Day 361 in the MEDI8897 gps, only 58.1% of infants had a ≥3-fold rise from baseline. One assumes that the MEDI8897 subjects would have had the same exposure to actual RSV, but why they did not have a corresponding increase in anti-RSV nAb titres is unknown, it seems unlikely at this juncture that the passive immunotherapy would have blunted an immune response to actual RSV infection.

19.1.2. Synopses of population pharmacokinetics analyses

19.1.2.1. PopPK analysis ID

The final version (30-Aug-2022) of the **MODELING AND SIMULATION REPORT POPULATION PK MODELING OF NIRSEVIMAB IN TERM AND PRETERM CHILDREN, AND EXTRAPOLATION TO HIGHER RISK CHILDREN** (see **m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep)**. The previous popPK model for nirsevimab was built on serum PK data from healthy adults and preterm infants in Phases 1, 1b/2a, 2b, and 3 studies (**Studies -1, -2, -3, MELODY, and MEDLEY**). The overall aim of the analyses is to support the dosing strategy of nirsevimab and the extrapolation of efficacy to the high-risk pop'n based on PK. The main objectives were as follows:
1. Update an existing popPK model based on phase 1, 1b/2a, 2b, 2/3, and 3 data evaluating the PK of nirsevimab serum conc'ns with additional pediatric data in late preterm and term infants entering their first RSV season (**MELODY**) and preterm infants with or without CLD/ CHD, entering their first and/or second RSV season (**MEDLEY**) to derive individual nirsevimab exposures (**MELODY, MEDLEY**).
2. Assess the success of the extrapolation via both the plan outlined in the approved EMA PIP of efficacy in the **MEDLEY** pop'n based on nirsevimab exposures (i.e., whether the proposed dose, 200 mg in Season 2, in the target palivizumab pop'n result in efficacious exposures in >80% of the **MEDLEY** pop'n), and comparison of serum conc'ns at the end of the RSV season (Day 151) in **MEDLEY** to those in **MELODY**, where efficacy was demonstrated.
3. Predict nirsevimab serum conc'ns in IC infants and children ≤24 mths of age in **MUSIC**.
Nirsevimab serum conc'n data from studies **Studies -1, -2, -3, MELODY**, and **MEDLEY** (seasons 1 and 2) are described by a 2- compartment PK model with covariate effects for body weight, postmenstrual age, race, ADA, and RSV season (1 or 2). Based on popPK analyses, exposures in the palivizumab-eligible pop'n (**MEDLEY**) were similar across subgps for CHD, CLD, and infants <29 wks GA. Extrapolation of efficacy and safety was achieved for the proposed dose (200mg in Season 2), in the target pop'n. $AUC_{baseline\ CL}$ were above the target in >80% of the overall pop'n in the **MEDLEY** second season (93.2%) and for subgps of special interest including infants with CLD (93.9%), and infants with haemodynamically significant CHD (91.4%). Additionally, Day 151 serum conc'ns in **MEDLEY** were comparable to those in **MELODY** across subgps in Season 1 (CHD, CLD, extremely pre-term <29 wks GA). In Season 2, children with CHD or CLD receiving 200mg nirsevimab achieved Day 151 serum conc'ns in the same range or slightly higher than those in MELODY.
Weight band dosing (50 mg <5 kg; 100 mg ≥5 kg) is predicted to be appropriate for infants ≥1 kg in their first RSV season. Simulations showed that 200mg dosing for the second RSV season results in exposures within the safe and efficacious range. The popPK model adequately predicted data in immunocompromised children entering their first or second RSV season in **MUSIC**, supporting comparable exposures to those in late preterm-to-term infants without immuncompromised conditions in **MELODY**. Overall, 48/59 (81.4%) subjects in **MUSIC** achieved exposures ($AUC_{baselineCL}$) above the target for efficacy; 28/35 (80.0%) in Season 1 (50mg/100mg weight-band dosing), and 20/24 (83.3%) in Season 2 (200mg).

Modeling datasets were provided to Certara by AstraZeneca via secure File Transfer Protocol site set up by Certara. The source data included dosing information, PK sampling information, demographics, clinical lab values, and other covariate information collected in the clinical studies included in this Application. Nirsevimab serum conc'ns were determined using a validated assay with a LLOQ of 0.5 µg/mL.

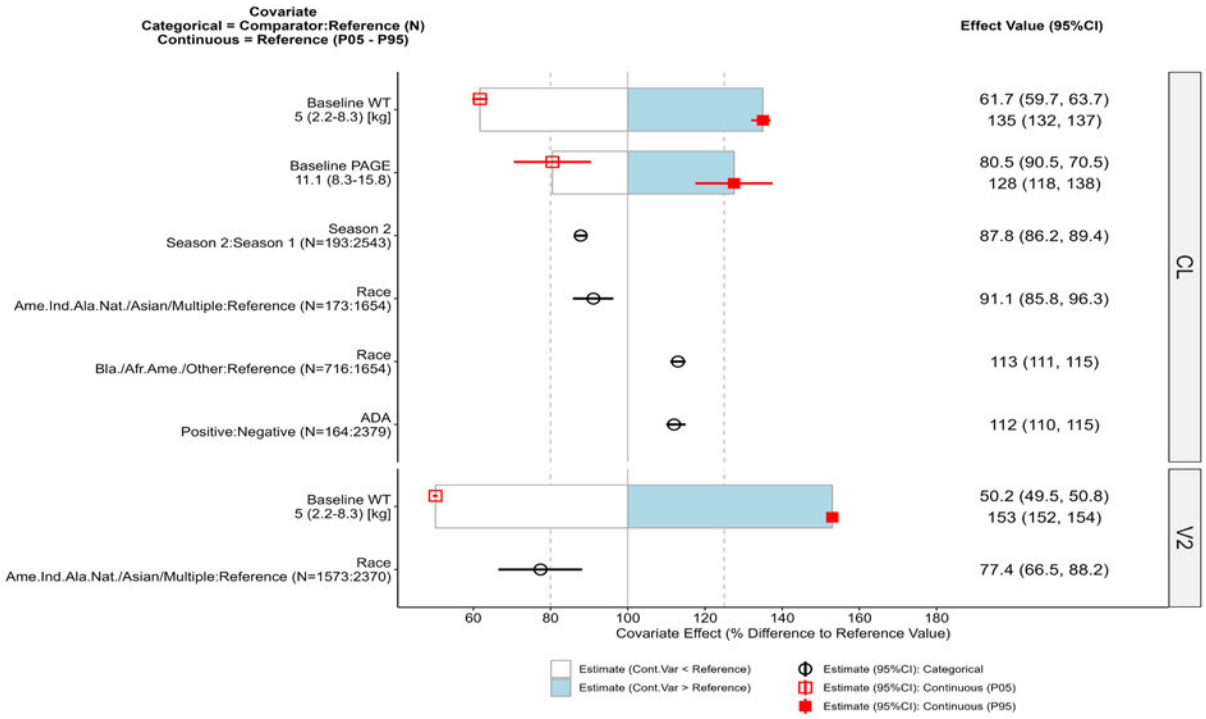
Evaluable subjects: For the popPK analysis, a subject was defined as evaluable if both of the following criteria were satisfied:
1. Received at least 1 dose of nirsevimab (as-treated pop'n); 2. Had at least 1 measurable nirsevimab conc'n observation with associated sampling time and dosing information

Covariate (Abbreviation) Description and/or Derivation
Body weight (WT) as a Time-varying covariate
Postmenstrual age (PAGE) as a Time-varying covariate: sum of gestational age at birth and postnatal age in mths
Japanese (JPN) – as a covariate of Japanese status
Race (RACE) - Race
CLD, covariate is the presence of chronic lung disease status (CHDCLD=2)
CHD status, covariate is the presence of congenital heart disease (CHDCLD=1 or 3)
Incidence of anti-drug antibody response (ADACAT, ADAFLG), covariate of Anti-drug antibody response (positive/negative) time constant (ADACAT) and/or time varying (ADAFLG)
Modeling and Simulation Analyses
The analyses were carried out according to the US Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/ PopPK-pharmacokinetics (accessed 30-Mar-2022)), US Guidance for Industry: Exposure Response (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072109.pdf (accessed 03-Apr-2019)), and the EU Guidance on Reporting the Results of PopPK Analyses (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf [Accessed 3rd April 2019).
Software: Nonlinear mixed-effects modeling software (NONMEM® version 7.4.3), a software package for nonlinear mixed-effects analysis (ICON, Hanover, MD, US), was used for popPK modeling. R (R Core Team [2020]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) was used for simulations, graphical analysis, model diagnostics, and statistical summaries. Perl-Speaks- NONMEM (PsN; Department of Pharmacy, Uppsala University, Uppsala, Sweden, vn. 4.8.1) was also used for facilitation of NONMEM tasks, such as covariate testing.

For a covariate to be included in the formal covariate analysis, the following needed to be met:
• The covariate was available in at least 80% of subjects;
• For categorical covariates, a minimum nos. of 15 subjects was in each category;
• If covariates (other than weight and age, which were included a priori) show a correlation of >0.5, only one of the correlated covariates was included in the formal analysis. This was either the covariate with the strongest influence, as determined by exploratory graphical analysis or the variable that was most meaningful from a clinical, biological, or practical perspective. Continuous covariates were preferred over categorised covariates with the same meaning.
Evaluation of the Final PopPK Model – is described in **the pop-ananlysis-report-2022 (module 5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\modeling-and-simulation-report)**
PK Data: Included 9597 measurable PK observations from 3133 subjects. Rich conc'n-time profiles were available in 102 adult subjects in **Study 1** after IV (n=18) and IM (n=84) dosing. Sparse data were available in 3053 subjects. The nirsevimab dose range was 10 to 3000 mg single dose. There were 4 subjects in the **MEDLEY** study who, by mistake, received a second dose of nirsevimab. There was also a single subject in the **MEDLEY** study who was mistakenly given a single dose of 67 mg. There were 4 subjects <5 kg who mistakenly received a 100 mg dose. There were 11 subjects >5 kg who mistakenly received a 50 mg dose. There were 2 subjects in **MEDLEY** Season 2 who, by mistake, were given a dose of 150mg. The longest exposure was 783 days. 1030 PK observations and 499 subjects were excluded from the analysis. The popPK analysis was conducted on a database containing 2683 subjects and 8987 PK observations.
Model Predictions for MUSIC: The final popPK model was used to perform a Bayesian Posthoc prediction of the PK data in MUSIC. Visual predictive check plots, generated by simulating from

the final model (n=1000 replicates) and overlaying observed PK profiles from IC children ≤24 mths of age in MUSIC. Overall, model predictions of **MUSIC** were adequate, given limited data. **MEDLEY:** Summaries of median simulated exposure metrics for infants in the lowest weight in each dose group are shown in **Table 31.** Successful extrapolation of efficacy was demonstrated in the overall **MEDLEY** Season 2 pop'n; a single 200 mg dose nirsevimab resulted in 93.2% of infants having $AUC_{baseline\ CL}$ above the target exposure threshold, (infants with CLD: 93.9%, infants with hemodynamically significant CHD: 91.4%). Summaries of the extrapolation results are provided in **Table 32**. Day 151 serum conc'ns and model predicted $AUC_{0\text{-}365}$ for the subgps of interest in Season 1 (CHD, CLD, extremely preterm <29 wks GA) are within the range of exposures in **MELODY**. In children with CHD or CLD receiving 200 mg nirsevimab in RSV Season 2, serum conc'ns Day 151 were in the same range and slightly higher vs. those in **MELODY**.

Figure 9. Forest Plot of Covariate Effects in Paediatric Subjects for the Final PopPK Model



Source: ASTR-NIRSE-run-plots-bla-Aug2022.R (run443). Notes: Vertical dashed lines are the range of effect considered to be clinically insignificant. Reference race= White or Native Hawaiian/Pacific Islander; Abbreviations: Ame.Ind./Ala.Nat.=American Indian or Alaskan Native; Bla./Afr.Ame.=Black or African American; N=number of subjects with available information; P05=5th percentile; P95=95th percentile; PAGE=postmenstrual age; V2=Vc=central volume of distribution; WT=body weight; P05=5th percentile, P95=95th percentile

Table 31. Median-Predicted Exposures for Lowest Weight Subjects per Dose and adult max. 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

Compared with an infant weighing 5 kg and receiving a 100 mg dose, the smallest infants (1 kg) are predicted to have ~84% higher C_{max}, ~9% lower concentrations at Day 151, and ~25% higher $AUC_{0\text{-}365}$ (Table 12). The lowest weight simulated subjects in Season 2 (6.5 kg) were predicted to have ~39% higher C_{max}, ~85% higher concentrations at Day 150, and ~68% higher $AUC_{0\text{-}365}$ than a 5kg infant receiving 100mg. For all 3 infant doses, $AUC_{0\text{-}365}$ and C_{max} are predicted to be substantially lower than the exposure observed for the highest dose tested in adults (3000mg IV).

Table 32. Extrapolation Results for Paediatric Season 2 Subjects in MEDLEY Stratified by CHD/CLD Status

	CHD (N=58)	CLD (N=132)	Total (N=190)
$AUC_{baseline\ CL} \geq$ Target	53 (91.4%)	124 (93.9%)	177 (93.2%)
$AUC_{baseline\ CL} <$ Target	5 (8.6%)	8 (6.1%)	13 (6.8%)

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

CONCLUSIONS

• PK of nirsevimab following IV and IM administration well characterised by a 2- compartment model with first-order absorption and elimination.
• The typical infant in Season 1 is White, weighing 5 kg, is ADA negative, with postmenstrual age of 11.1 mths at the time of dose. Parameters for a typical infant are as follows: CL = 3.42 mL/day, V2 = 216 mL, Q = 150 mL/day, and V3 = 261 mL.
• The mean terminal $t_{½}$ in infants is 71.4 days.
• IM bioavailability was 84% based on adult data.
• Covariate effects as follows:
− Body weight: Allometric exponent was 0.589 for CLs (CL and Q) and 0.84 for volumes (V2 and V3)
− Postmenstrual age effect on CL: Fractional CL at 40 wks GA (BETACL): 0.364; Maturation $t_{½}$ (TCL): 14.8 mths
− Race effects on CL and V2: Black, African American, or Other: 13% higher CL; Asian, American Indians, Alaskan Natives, or Multiple Races: 8.9% lower CL; 23% lower V2
− ADA: Subjects with ADA had 12% higher CL
− Season 2: CL 12% lower than expected based on other covariates

Simulation

• Weight-band dosing (50 mg <5 kg; 100 mg ≥5 kg) is predicted to be appropriate for infants ≥1 kg in their first RSV season.
• The 200 mg dose in Season 2 results in exposures within the range of safe and efficacious exposures.

Extrapolation to MEDLEY Season 2

• Based on popPK analyses, exposures in the palivizumab-eligible pop'n (**MEDLEY**) were similar across subgps for CHD and CLD.
• Extrapolation of efficacy and safety was achieved; $AUC_{baseline\ CL}$ was above the target in >80% of the **MEDLEY** Season 2 pop'n (93.2%) and for infants with CLD (93.9%), and infants with haemodynamically significant CHD (91.4%).
• Serum nirsevimab conc'ns at Day 150 across **MEDLEY** subgps in Season 1 (CHD, CLD, extremely preterm <29 wks GA) were comparable to those in **MELODY**. In children with CHD or CLD receiving 200 mg nirsevimab in RSV Season 2, serum conc'ns Day 151 were in the same range and slightly higher compared to those in **MELODY**.

Prediction and Extrapolation in Immunocompromised Children (MUSIC)

• The popPK model adequately predicts the data in children IC conditions, supporting comparable exposures to those in late preterm to term infants without IC condition in **MELODY**.
• Children with IC conditions receiving weight-band dosing in Season 1, or 200 mg in Season 2, achieve nirsevimab serum conc'ns Day 151 comparable to those in **MELODY**.
• Overall, 48/59 (81.4%) subjects achieve exposures ($AUC_{baselineCL}$) above the target for efficacy; 28/35 (80.0%) in Season 1 and 20/24 (83.3%) in Season 2

20. Attachment: additional evaluation material

21. Information about the evaluator

s22

Appendix: study summary and commentary

Therapeutic Goods Administration

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Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Advisory Committee on Medicines Minutes

Item 2.03
nirsevimab

Proprietary Product Name: BEYFORTUS

Sponsor: Sanofi-Aventis Australia Pty Ltd

October 2023

Contents

Submission details

Submission details	
Type of submission:	Type A – New biological entity
Product name:	BEYFORTUS
Active ingredient:	nirsevimab
Submission number:	PM-2022-04428-1-2
Proposed strength(s) / dose form(s):	BEYFORTUS 50 mg solution for injection in prefilled syringe BEYFORTUS 100 mg solution for injection in prefilled syringe
Initial indication proposed by the sponsor:	BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: (i) Neonates and infants entering or 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, which may include but is not limited to children with: - Chronic lung disease of prematurity (CLD) - Haemodynamically significant congenital heart disease (CHD) - Immunocompromised states - Down syndrome - Cystic fibrosis - Neuromuscular disease - Congenital airway anomalies. BEYFORTUS should be used in accordance with available official recommendations.

Submission details	
Proposed dosage:	Dosing recommendations <u>Infants entering their first RSV season</u> The recommended dose is a single fixed dose of 50 mg for infants with body weight <5 Kg and a single fixed dose of 100 mg for infants with body weight ≥5 Kg. BEYFORTUS should be administered from birth for infants born during the RSV season. For others born outside the season, BEYFORTUS should be administered ideally prior to the RSV season. <u>Children who remain vulnerable to severe RSV disease entering their second RSV season</u> The recommended dose is a single dose of 200 mg given as two intramuscular (IM) injections (2 x 100 mg). For individuals undergoing cardiac surgery with cardiopulmonary bypass, it is recommended that an additional dose is administered as soon as the individual is stable after surgery to ensure adequate nirsevimab serum levels. If within 90 days after receiving the first dose of BEYFORTUS, the additional dose during the first RSV season should be 50 mg or 100 mg according to body weight, or 200 mg during the second RSV season. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight during the first RSV season, or 100 mg during the second RSV season, to cover the remainder of the RSV season.

Documents submitted for ACM consideration

The ACM considered the following documentation:

Papers presented for consideration

A1 Delegates Summary and Request for ACM Advice
A1a Literature - Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants (Griffin et al.,NEJM 2020)
A1b Literature - Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants (Hammitt et al.,NEJM 2022)
A1c Literature - Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants (Hammitt et al,NEJM, 2023)
A1d Literature - Efficacy of nirsevimab - pooled analysis (Simões et al,Lancet 2023)
A1e Literature - Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity (Domachowske et al,NEJM, 2022)
A2 Sponsors Application Letter
M3 Quality (Biological Medicines) Summary of Evaluation
M4 Nonclinical Summary and Evaluation
M5 Clinical Evaluation Report
M5a Clinical Evaluation Report - PopPK Review
M5b Clinical Evaluation Report - FDA Integrated Review
R1 Risk Management Plan (RMP) Evaluation Report

Sponsor response documents
A3 Sponsors Response to Delegates Overview (Cover Letter)
A3a Sponsors Response to Delegates Overview
A3ai Sponsors Response to Delegates Overview
A3b Foreign Regulatory Status
A3c Adverse Reactions Update
A3d Sponsors Comments on PI
A3e Sponsors Comments on Foreign PI
A3f PSUR for the period 31 October 2022 to 30 April 2023
A3g Literature - Edwards, Pediatrics (2021)
A3gi Literature - Fenton, BMC Pediatrics (2013)
A3gii Literature - Manzoni, Infect Dis Ther (2017)
A3giii Literature - Thorburn, Arch Dis Child (2009)

Product information documents
C1 Product Information - annotated
C1 Product Information - clean
C1a Consumer Medicines Information - annotated
C1a Consumer Medicines Information - clean
C2 Approved European Summary of Product Characteristics
C2a Approved US Package Insert
C2b Approved Canadian Product Monograph

Delegate's Overview

Delegate's summary of issues

The Delegate identified the following in their request for ACM advice:

The clinical data package for this submission included three pivotal, double-blind, randomised studies (Study 3 [D5290C00003], MELODY [D5290C00004] and MEDLEY [D5290C00005]) and an open-label study in immunocompromised infants/children (MUSIC [D5290C00008]).

In addition, there were two completed dose-escalation, safety, PK and anti-drug antibody studies (Study 1 [D5290C00001] and Study 2 [D5290C00002]), which (along with MELODY, Study 3, and MEDLEY) contributed data for population PK modelling.

The submitted data are sufficient to recommend approval. Areas of uncertainty include the low number of subjects in the MEDLEY and MUSIC studies and the extrapolation of efficacy to high-risk subgroups.

Delegate's preliminary view

While a decision is yet to be made, at this stage the Delegate is inclined to approve the registration of the product.

The final wording of the indication will be confirmed following ACM advice.

If registration was approved, the Delegate would propose the following additional conditions of registration:

- Quality and RMP conditions of registration

Advice sought by Delegate of the Secretary of Department of Health and Aged Care

1. Please comment on the findings of the MEDLEY study, in light of the proposed indication and dosing for children entering their second season of RSV and the low number of subjects in this study.
2. Related to point 1, does the ACM agree with extrapolation of efficacy to each of the high-risk groups included in the proposed indication, based on the inclusion criteria and results of the MEDLEY and MUSIC studies? What is the view of the ACM regarding the alternative wording of the indication proposed by the Delegate?
3. Does the ACM have concerns with using BEYFORTUS routinely in all infants during their first RSV season?
4. Related to point 3, in what settings does the ACM anticipate that BEYFORTUS will be administered to infants? Will this occur in hospital clinics, local immunisation clinics and general practices?
5. The ACM is also requested to provide advice on any other issues that it thinks may be relevant.

ACM discussion

An invited expert in the field of paediatric infectious diseases and immunisation was involved in the discussion for this item.

General comments

Respiratory Syncytial Virus (RSV) is a common cause of lower respiratory tract infection, particularly bronchiolitis, in infants. Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2 years. 2-3% of young infants will be hospitalised for RSV, with the highest RSV hospitalisation rates in first months of life. The ACM noted the significant burden of disease associated with RSV associated hospitalisation.

The ACM examined RSV disease prevention options and noted that there are currently no registered RSV vaccines. It was noted that palivizumab is currently registered for high-risk infants and requires monthly injections during the RSV season.

The ACM noted that nirsevimab is a recombinant human IgG1k monoclonal antibody. It has neutralising activity against both RSV subtypes A and B engineered with a triple amino acid substitution (M252Y/S254T/T256E [YTE]) in the Fc region to prolong serum half-life of the antibody. Nirsevimab inhibits the essential membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

International regulatory status

The ACM noted similar applications have been approved in Canada (April 2023), the European Union (October 2022), Great Britain (November 2022) and the United States of America (July 2023). It was also noted that applications are currently under consideration in Japan and Switzerland.

Within the USA, the ACM noted that the Advisory Committee on Immunization Practices (ACIP) recommends use for infants aged less than 8 months born during or entering their first RSV season and for infants aged 8 to 19 months at increased risk of severe RSV disease entering their second RSV season.

Efficacy

The clinical data package for this submission includes three pivotal, double-blind, randomised studies (Study 3, MELODY and MEDLEY) and an open-label study in immunocompromised infants/children (MUSIC).

The ACM noted that overall, the clinical studies were clear and comprehensive and were either placebo controlled or included palivizumab as a comparator for at risk populations. The ACM also noted that some studies were impacted by the pandemic.

Study 3 was a Phase 2/2b study in preterm infants aged 29 to less than 35 weeks to determine if nirsevimab would be efficacious in reducing medically attended RSV-confirmed lower respiratory tract infection (LRTI) in healthy preterm infants entering their first RSV season. The ACM noted a relative risk reduction (RRR) in the incidence of medically attended (MA) RSV-confirmed LRTI of 70.1% (95% CI: 52.3% to 81.2%) when compared to placebo ($p < 0.0001$).

MELODY was a Phase 3 study in infants aged ≥35 weeks who were entering their first RSV season to determine if nirsevimab will prevent MA RSV LRTI. The ACM noted the number needed to treat (NNT) to prevent one hospitalisation for LRTI of any cause was 53.1 (95% CI, 29.4 to 250.0), further noting this result was similar to the primary cohort in the trial (this cohort was based on the Primary Analysis in Intention-to-treat Population 1)

MEDLEY was a Phase 3 study in high-risk infants entering their first or second RSV season to determine if nirsevimab will prevent MA RSV LRTI. The ACM noted that in this study high risk included preterm infants and infants with chronic lung disease of prematurity (CLD) / haemodynamically significant congenital heart disease (CHD). The ACM noted that the season 1 nirsevimab population included approximately 600 children (400 in the preterm cohort and 200 in the CLD/CHD cohort). The season 2 nirsevimab population comprised of approximately 200 children from the CLD/CHD cohort who had already participated in season 1. The ACM noted the lower season 2 enrolments and that there were no instances of MA RSV LRTI through to 150 days post first dose in season 2 in any treatment group (palivizumab/palivizumab group, palivizumab/nirsevimab group and nirsevimab/nirsevimab group).

Safety

Overall safety data were available from 3680 children dosed with nirsevimab (3284 children receiving the proposed dose). All and combined analysis showed minimal reactogenicity. The ACM noted that in general, the safety profile of nirsevimab appears appropriate however noted that these studies were undertaken during the pandemic when significant public health measures were in place.

The ACM noted the results from the MUSIC study, a Phase 2 open label, uncontrolled study in immunocompromised children ≤24 months of age at time of administration. The primary objective was to evaluate the safety and tolerability of nirsevimab within this population.

The ACM noted 925 infants were enrolled including 310 in the CHD/CLD cohort and 615 in the preterm cohort. Two adverse events of special interest were noted in the nirsevimab group: heparin-induced thrombocytopenia in an infant with CHD and maculopapular rash following a placebo dose in a preterm infant. In general, infants with CHD or CLD and in those born preterm, the safety profile of nirsevimab was similar to that of palivizumab.

The ACM also noted the safety results from the two season MEDLEY study which evaluated the safety of both palivizumab and nirsevimab. The study showed nirsevimab had a

comparable safety and tolerability profile to palivizumab, there was no evidence of immune priming in patients who had received prior nirsevimab and no evidence that the second dose of nirsevimab boosted anti-drug antibody (ADA) responses in ADA positive to nirsevimab children in season 1. There was no apparent impact of ADA against nirsevimab on pharmacokinetics and efficacy.

The ACM discussed the potential for a reduction in virus susceptibility and noted that overall, >99% of isolates from the Phase 2b and MELODY studies retained susceptibility to nirsevimab[1].

Risk Management Plan

The ACM noted the following limitations with the current data set:

- Long term safety and efficacy/effectiveness in large populations
- Effectiveness in settings with greater RSV transmission
- Efficacy/effectiveness by older age at peak RSV season/exposure
- Resistant RSV strains/mutations

ACM advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. ***Please comment on the findings of the MEDLEY study, in light of the proposed indication and dosing for children entering their second season of RSV and the low number of subjects in this study.***

The ACM highlighted the need to protect children up to 24 months who remain vulnerable to severe RSV disease. While the ACM noted the low number of children receiving a second dose of nirsevimab in season 2 within the MEDLEY study, the ACM was of the view that this should not impact on the proposed indication.

The ACM noted that the MEDLEY study demonstrated comparable safety in season 2 and that there were no instances of medically attended RSV LRTI through to 150 days post first dose in season 2 in any treatment group. The ACM did however note that the outcomes were potentially impacted by the COVID-19 public health measures.

In providing this advice, the ACM highlighted the need for robust post market studies of safety and effectiveness post registration and effective long term RSV disease surveillance.

The ACM noted that the time of administration of the season 2 dose was able to be controlled in the MEDLEY study and agreed that in clinical practice administration may be dependent on the timing of the RSV season and/or the interpretation of what is an 'RSV season'. Considering this, the ACM was supportive of the dosing recommendations not including a minimum interval between doses.

[1] Ahani, B., Tuffy, K.M., Aksyuk, A.A. *et al.* Molecular and phenotypic characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. *Nat Commun* **14**, 4347 (2023). https://doi.org/10.1038/s41467-023-40057-8

2. ***Related to point 1, does the ACM agree with extrapolation of efficacy to each of the high-risk groups included in the proposed indication, based on the inclusion criteria and results of the MEDLEY and MUSIC studies? What is the view of the ACM regarding the alternative wording of the indication proposed by the Delegate?***

The ACM supported the extrapolation of efficacy to each of the high-risk groups included in the proposed indication. The ACM advised that there is a favourable risk benefit profile for high-risk groups in both RSV season 1 and season 2.

The ACM noted that the population pharmacokinetic model adequately predicted nirsevimab concentrations in children, suggesting comparable exposures in high-risk groups. Further noting that these assumptions are biologically plausible (same virus, same mechanism of action, similar expected exposure response relationship and safety).

The ACM commented on the higher concentrations in season 2 and noted that this may reflect the different population, sparse sampling and differences in absorption from the injection site that are not appreciated in the model.

The ACM discussed the proposed indications and advised that simpler wording as proposed below could be appropriate assuming that 'high risk / at risk children' is clearly defined within clinical guidance.

Proposed indication:

> *BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in:*
>
> *- Neonates and infants born during or entering their first RSV season.*
>
> *- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.*
>
> *BEYFORTUS should be used in accordance with official recommendations.*

The ACM strongly supported the inclusion of the statement "used in accordance with official recommendations" and noted it would be important to have information available in the Australian context, e.g., in the Australian Immunisation Handbook and/or other guideline.

3. ***Does the ACM have concerns with using BEYFORTUS routinely in all infants during their first RSV season?***

The ACM stated that the safety and efficacy profile appears appropriate and does not have concerns with using Beyfortus routinely in all infants during their first RSV season.

The ACM indicated that the available data does not suggest 'rebound' of higher incidence or more severe disease later in infancy or in the second year of life and there is potential for broad impact on RSV disease within Australia. The ACM also advised that use in all infants is a suitable indication, as it can be challenging to identify infants at risk of RSV hospitalisation noting that many who require hospitalisation due to RSV do not have risk factors.

The ACM also noted emerging evidence that suggests that while nirsevimab protects from RSV disease new evidence suggests RSV infection still occurs, inducing immune response

which can lay an important foundation for future immune boosting with infection in subsequent seasons[2].

4. Related to point 3, in what settings does the ACM anticipate that BEYFORTUS will be administered to infants? Will this occur in hospital clinics, local immunisation clinics and general practices?

The ACM noted that it would be reasonable and most practical to administer Beyfortus at birth (for example, with the hepatitis B vaccine), or at routine immunisation visits at 2, 4 or 6 months. The ACM did not highlight any concerns with concomitant administration of Beyfortus with other vaccines, other than the need for an additional intramuscular injection.

The ACM noted that while it is likely suitable to administer Beyfortus at routine immunisation appointments, this practice has the potential to increase burden on GPs and vaccination clinics and this will need to be appropriately considered.

The ACM highlighted that the timing of the RSV seasons will also need to be considered to ensure timely administration. It is likely that systems and guidelines will need to be established to manage this appropriately.

The ACM reiterated the need for clear and up to date clinical guidelines that define high risk children and give consideration to administration timelines.

5. The ACM is also requested to provide advice on any other issues that it thinks may be relevant.

The ACM suggested some updates to the Product Information, as proposed below:

Within the Dose and Method of Administration – Dosing recommendations section (page 2 of the annotated version dated 20Sep23) the ACM noted that it would be appropriate to more explicitly state that the two IM injections can be administered on the same day. The ACM proposed:

> *For children up to 24 months of chronological age who remain at increased risk for severe RSV disease in their second RSV season, the recommended dosage of BEYFORTUS is a single 200 mg dose administered as two IM injections (2 x 100 mg) at the same visit.*

Within the same section (page 3 of the annotated version) the ACM proposed an update to the limited data statement as below:

> *Limited data or no data are available in infants with a range of underlying conditions, e.g. Down syndrome (n=13), Cystic fibrosis (n=5), Congenital airway anomalies (n=9), and Neuromuscular disease (n=0; not evaluated in clinical trials).*

Within the Pharmacology Properties section (page 8 of the annotated version) the ACM indicates that the term 'Virus resistance' could be used instead of 'Antiviral resistance'.

In the Consumer Medicines Information, the order of health professionals in Section 4 needs to match the order in Sections 3 and 6.

[2] Wilkins, D., Yuan, Y., Chang, Y. *et al.* Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants. *Nat Med* **29**, 1172–1179 (2023). https://doi.org/10.1038/s41591-023-02316-5

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *BEYFORTUS is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in:*
>
> *- Neonates and infants born during or entering their first RSV season.*
>
> *- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.*
>
> *BEYFORTUS should be used in accordance with official recommendations.*

Ratified and sent to the sponsor on 23 October 2023.

Therapeutic Goods Administration

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