Clinical Study Report Synopsis – Final Analysis

Drug Substance	Nirsevimab (MEDI8897)
Study Code	D5290C00005
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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)

Study dates:	First subject enrolled: 30 July 2019 Last subject last visit: 20 January 2023 The analyses presented in this report are based on database lock date of 22 February 2023 for the Final Analysis.
Phase of development:	II/III
International Co-ordinating Investigator:	Not applicable
Sponsor's Responsible Medical Officer:	[redacted] [redacted] AstraZeneca BioPharmaceuticals R&D Gaithersburg, MD

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

Study Centre(s)

Subjects in Season 1 were dosed at 126 centres in 25 countries.

Subjects in Season 2 were dosed at 58 centres in 18 countries.

Publications

Domachowske J, Madhi SA, Simões EAF, Atanasova V, Cabañas F, Furuno K, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. N Engl J Med. 2022;386(9):892-4.

Objectives and Criteria for Evaluation

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

ADA = anti-drug antibody; AESI = adverse event of special interest; CHD = congenital heart disease; CLD = chronic lung disease; CSR = clinical study report; IM = intramuscular(ly); 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.

Exploratory objectives and endpoint measures are presented in the CSR body.

Study Design

Study D5290C00005 (MEDLEY) was a pivotal Phase II/III 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). It was planned to enrol approximately 900 palivizumab-eligible infants entering their first RSV season into 1 of 2 cohorts: (1) preterm cohort, including approximately 600 preterm infants (≤ 35 weeks gestational age [wGA]) 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). Note that in Japan, the CLD/CHD cohort included subjects with Down syndrome alone who are palivizumab-eligible in this country.

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.

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.

To ensure the blinding of Season 2 treatment assignment for CLD/CHD subjects who were randomised to the palivizumab group in Season 1, any data with potential unblinding risk were split by Season 1 and Season 2 by the corresponding third-party data vendors and when the primary database lock occurred, only unblinding data from Season 1 were transferred to the Sponsor for analysis. Regardless of season, site personnel, participants, and the study team members who participated in the advice or decisions involving study subjects and/or day-to-day interactions with the site, remained blinded until the end of the study to ensure the trial integrity was maintained.

This Final CSR presents results from the following analyses:

- The Final Analysis presents safety, efficacy, PK, and ADA data at the time of the database lock (DBL) (22 February 2023). It 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).

The key analyses, study populations, data cut-off (DCO), and follow-up periods are summarised in Table 7 of the CSR body.

Target Population and Sample Size

The target population comprised palivizumab-eligible infants, including preterm infants ≤ 35 weeks 0 days gestational age without CHD or CLD entering their first RSV season (preterm cohort) and children with CLD and/or CHD entering their first RSV season (CLD/CHD cohort).

Subjects in the Season 1 CLD/CHD cohort proceeded to the Season 2 phase of the study; those who received nirsevimab in Season 1 were assigned to receive nirsevimab again in Season 2 (NIRS/NIRS group); subjects who received palivizumab in Season 1 were subsequently re-randomised to nirsevimab (PALI/NIRS group) or palivizumab (PALI/PALI group) in Season 2.

With respect to safety, 600 subjects exposed to nirsevimab in Season 1 was to provide a 95% probability of observing at least one adverse event (AE) if the true event rate is 0.5%; if no AEs were observed, this study provided 95% confidence that the true event rate would be < 0.5%. The sample size was set based on safety considerations.

With respect to descriptive efficacy data, approximately 600 subjects were exposed to nirsevimab and 300 subjects were exposed to palivizumab in Season 1 to observe numerically similar efficacy for both monoclonal antibodies. Using an assumption of a 6% RSV lower respiratory tract infection (LRTI) rate in palivizumab recipients, approximately 18 events were to be observed in that group. Assuming a 6% rate of RSV LRTI in nirsevimab recipients, 600 nirsevimab subjects in Season 1 were to provide approximately 36 events in that group. However, because of the largely reduced RSV circulation due to COVID-19 pandemic-related measures, the observed event rates could be much lower.

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

In Season 1, nirsevimab was administered as a single fixed IM dose of 50 mg for infants weighing < 5 kg or 100 mg IM for infants weighing ≥ 5 kg followed by 4 once-monthly IM doses of placebo (0.9% saline).

In Season 2, nirsevimab was administered as a single fixed IM dose of 200 mg (as 2 injections of 1 ml at separate sites) followed by 4 once-monthly IM doses of placebo (0.9% saline).

In both seasons, palivizumab was administered as 5 once-monthly IM doses of 15 mg/kg.

Refer to Table 3 of the CSR body for lot numbers used in this study.

Duration of Treatment

In both seasons, duration of treatment was 5 months; in each season nirsevimab was administered as a single dose.

Statistical Methods

There were 3 planned analyses for this study: the Primary Analysis, Season 2 Analysis, and Final Analysis. Results from the Final Analysis are presented in this Final CSR.

The Primary Analysis was conducted after all randomised subjects had completed follow-up through the first 5-month RSV season (ie, Season 1 Day 151 visit). This analysis included all available Season 1 safety, efficacy, PK, and ADA data at the time of the DCO (03 May 2021) through at least 150 days post first dose. Note that due to the late arrival of samples to the testing laboratory, which were deemed critical to the Primary Analysis, the data transfer provided by the third-party vendor, including PK and ADA results, was conducted in 2 cumulative transfers, resulting in 2 database lock dates (10 June 2021 and 19 July 2021). This allowed PK modelling to commence and minimise the impact on timelines of further deliverables dependent on these data.

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-month RSV season (ie, 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 April 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 (ie, through 360 days post first dose [the end of Season 1]).

The Final Analysis was conducted after all subjects had completed the last visit of the study (ie, through 360 days post first dose in Season 2), and included all data collected in the study.

Safety of nirsevimab was summarised by treatment group based on the As-treated Population, defined as all subjects who received any investigational product (IP) analysed according to treatment received. For the Season 1 summary, the analysis dataset included subjects from the preterm and CLD/CHD cohorts, presented by the treatment received in Season 1 (ie, nirsevimab or palivizumab). For the Season 2 summary, the analysis dataset included subjects from the overall (ie, CLD/CHD) Season 2 population, presented by the treatment received in

Season 1 and Season 2 (ie, NIRS/NIRS, PALI/NIRS, or PALI/PALI). All safety variables were summarised descriptively between the nirsevimab and the palivizumab groups in Season 1 (through 360 days post first dose in Season 1) and between the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups in Season 2 (through 360 days post first dose in Season 2). In addition, for the NIRS/NIRS and PALI/PALI groups, selected outputs are provided for data combined from both seasons,

All efficacy summaries were based on the Intent-to-treat Population, defined as all randomised subjects analysed according to randomised treatment assignment. The incidence of medically attended (MA) RSV LRTI (inpatient and outpatient) through 150 days post first dose (ie, during a typical 5-month RSV season) in Season 1, based on RSV test results (performed centrally using real-time reverse transcriptase-polymerase chain reaction) and objective protocol-defined LRTI criteria, was summarised by Season 1 treatment group for all 900 subjects. The 95% confidence interval (CI) of the percentage of subjects who met this efficacy endpoint was presented by treatment groups (nirsevimab and palivizumab). Equivalent efficacy analyses were conducted through 150 days post first dose in Season 2 for NIRS/NIRS, PALI/NIRS and PALI/PALI groups.

Study Population

In Season 1, a total of 960 subjects were screened, of whom 35 were screen failures because they did not meet the eligibility criteria, withdrew consent, or met other reasons for withdrawal. 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). For the key subpopulations representing the unique populations in this study, 200 infants born < 29 wGA, 104 infants with CHD, and 217 infants with CLD were randomised. Overall, most 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]); 88.1% of nirsevimab subjects (543/616 subjects) and 85.1% of palivizumab subjects (263/309 subjects) completed the efficacy follow-up through 360 days post first dose (ie, completed Season 1).

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. Overall, the majority of subjects completed the efficacy follow-up through at least 150 days post first dose (97.8% [176/180 subjects], 100.0% [40/40 subjects], and 95.2% [40/42 subjects]) and (96.7% [174/180 subjects], 97.5% [39/40 subjects], and 95.2% [40/42] subjects) completed follow-up

through 360 days post first dose (ie, completed Season 2) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively.

The demographic and baseline characteristics of the study population were generally balanced between treatment groups in the overall population and the preterm and CLD/CHD cohorts. For subjects entering Season 1, the majority of subjects were White (79.2% [732/925 subjects]) and preterm (85.1% [787/925 subjects] < 35 wGA), median age at randomisation was 3.5 months (range, 0.07 to 12.25 months), and 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).

Summary of 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 with the current standard of care, palivizumab, in the overall population and preterm and CLD/CHD cohorts (Table S1), including infants with CLD, CHD, and those born < 29 wGA. The 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 adverse events of special interest (AESIs), and new onset chronic disease (NOCDs). There were no IP-related ≥ Grade 3 events, IP-related serious adverse events (SAEs), or IP-related NOCDs.

In the overall population, 444/614 subjects (72.3%) and 215/304 subjects (70.7%) in the nirsevimab and palivizumab groups, respectively, had at least one AE (Table S1). A majority of the events were of Grade 1 or Grade 2 severity. The most common AEs (> 10% of subjects) reported for nirsevimab (vs palivizumab) were upper respiratory tract infection (URTI; 24.3% [149/614 subjects] vs 26.0% [79/304 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 groups (1.6% [10/614 subjects] vs 2.0% [6/304 subjects]). The most common IP-related AEs (≥ 2 subjects in either group) 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 one AESI of hypersensitivity and 2 AESIs of thrombocytopenia: (1) rash maculo-papular (assessed as a skin hypersensitivity reaction), which occurred on the same day as a placebo IP dose, 92 days post first active dose of nirsevimab (and 61 days after the subject mistakenly received nirsevimab on Day 31); the event was considered IP-related and the subject was

withdrawn from IP the same day; (2) heparin-induced thrombocytopenia 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) thrombocytopenia, 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. Adverse events of special interest based on selected compatible MedDRA preferred terms (PTs) were generally similar between the nirsevimab and palivizumab groups in the overall population 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 group was numerically higher compared with the palivizumab group (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.

Adverse events through 30 days post first dose were evaluated as post-hoc analyses (ie, subsequent to the Primary Analysis) to permit an assessment of AEs relative to the active nirsevimab dose since subjects in the nirsevimab group received an active dose followed by 4 once-monthly placebo doses. The types and frequency of AEs within 30 days post first dose were generally balanced between the nirsevimab and palivizumab groups for the overall population 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 groups in the CLD/CHD cohort was not seen within all analysed time points through 30 days post first dose (ie, 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]) groups had IP-related skin reactions. These events were all of Grade 1 severity and included rash maculo-papular (assessed as a skin hypersensitivity reaction and recorded as an AESI by the investigator) and rash in the nirsevimab group and injection site induration and rash macular in the palivizumab group. Skin hypersensitivity reactions were reported by the investigator in one subject in the nirsevimab group: the aforementioned event rash maculo-papular in a subject in the preterm cohort who had no ADA detectable with available assessments through Day 361. This event was not consistent with immediate hypersensitivity based on the latency of onset after nirsevimab dose (92 days post first active dose of nirsevimab and 61 days after the subject mistakenly received nirsevimab on Day 31).

Treatment-emergent NOCDs were reported in 3 (0.5% [3/614]) subjects in the nirsevimab group: nonserious Grade 2 asthma in the preterm cohort on Day 192, serious Grade 2 calculus urinary in the CLD/CHD cohort on Day 101, and nonserious Grade 2 bronchopulmonary dysplasia (verbatim term: asthma, yes, worsening/exacerbation of underlying bronchopulmonary dysplasia) in the CLD/CHD cohort on Day 110. None of these 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; these infants all had serious, complex underlying medical conditions at baseline.

In the overall population, the frequency of SAEs was similar between the nirsevimab and palivizumab groups (13.0% [80/614 subjects] vs 12.5% [38/304 subjects]). The most common SAEs (> 2 subjects) reported for nirsevimab (vs palivizumab) were bronchiolitis (11 vs 4 subjects), gastroenteritis (6 vs 1 subjects), bronchitis (5 vs 2 subjects), pneumonia (5 vs 1 subjects), respiratory syncytial virus bronchiolitis (4 vs 2 subjects), and COVID-19 and viral URTI (3 vs 1 subjects each). None of the SAEs was considered by the investigator to be IP-related.

Table S1 Overall Summary of Treatment-emergent Adverse Events for Overall Population, Preterm and CLD/CHD Cohorts Through 360 Days Post First Dose in Season 1 – As-treated Population (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 event	215 (70.7)	444 (72.3)	141 (68.4)	287 (70.7)	74 (75.5)	157 (75.5)
Occurring ≤1 day post any dose	13 (4.3)	30 (4.9)	9 (4.4)	21 (5.2)	4 (4.1)	9 (4.3)
Occurring ≤3 days post any dose	38 (12.5)	77 (12.5)	27 (13.1)	52 (12.8)	11 (11.2)	25 (12.0)
Occurring ≤7 days post any dose	77 (25.3)	148 (24.1)	49 (23.8)	103 (25.4)	28 (28.6)	45 (21.6)
Occurring ≤14 days post any dose	139 (45.7)	248 (40.4)	88 (42.7)	167 (41.1)	51 (52.0)	81 (38.9)
≥1 IP-related event	6 (2.0)	10 (1.6)	4 (1.9)	6 (1.5)	2 (2.0)	4 (1.9)
≥1 event of ≥Grade 3 [b]	25 (8.2)	50 (8.1)	8 (3.9)	18 (4.4)	17 (17.3)	32 (15.4)
Occurring ≤1 day post any dose	1 (0.3)	1 (0.2)	1 (0.5)	0	0	1 (0.5)
Occurring ≤3 days post any dose	4 (1.3)	2 (0.3)	2 (1.0)	0	2 (2.0)	2 (1.0)
Occurring ≤7 days post any dose	5 (1.6)	6 (1.0)	3 (1.5)	1 (0.2)	2 (2.0)	5 (2.4)
Occurring ≤14 days post any dose	10 (3.3)	14 (2.3)	3 (1.5)	2 (0.5)	7 (7.1)	12 (5.8)
≥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)

Table S1 Overall Summary of Treatment-emergent Adverse Events for Overall Population, Preterm and CLD/CHD Cohorts Through 360 Days Post First Dose in Season 1 – As-treated Population (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 AESI based on selected MedDRA PT codes	47 (15.5)	116 (18.9)	32 (15.5)	67 (16.5)	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	3 (0.5)	0	1 (0.2)	0	2 (0.7)
≥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).

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

Treatment-emergent adverse events reporting period for Season 1 was from Season 1, Day 1 to Season 1, Day 361 or the last day prior to first dose of Season 2, whichever came earlier.

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; NOCD = new onset chronic disease; PT = preferred term.

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. Note that 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).

The incidence of AESIs based on selected MedDRA PTs was low and generally balanced between treatment groups in the CLD/CHD Cohort in Season 2 (Table S2). The incidence of ≥ Grade 3 events and SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group; however, this was not observed within all analysed time points through 30 days post first dose. 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. There were no deaths in Season 2.

In the CLD/CHD Cohort, 130/180 subjects (72.2%), 31/40 subjects (77.5%) and 29/42 subjects (69.0%) in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively, had at least one AE (Table S2). The majority of the events were of Grade 1 or Grade 2 severity. The most common AEs (> 10% of subjects in any treatment group) were URTI (26.7%, 20.0%, and 21.4%), rhinitis (16.1%, 15.0%, and 14.3%), nasopharyngitis (14.4%, 17.5%, and 21.4%), pyrexia (12.8%, 22.5%, and 14.3%), COVID-19 (8.9%, 7.5%, and 11.9%), viral URTI (8.3%, 20.0%, and 4.8%), otitis media acute (6.1%, 12.5%, and 4.8%), and diarrhoea (5.6%, 5.0%, and 16.7%), respectively.

There were no observed events of anaphylaxis or serious allergic reactions.

One AESI was reported by investigators in the NIRS/NIRS group: pancytopenia, considered unrelated to IP, 253 days post first active dose of nirsevimab. Adverse events of special interest based on selected MedDRA PTs were comparable between treatment groups in the CLD/CHD Cohort (15.6% [28/180 subjects], 12.5% [5/40 subjects], and 11.9% [5/42 subjects], in the NIRS/NIRS, PALI/NIRS, and PALI/PALI groups, respectively). 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.

For TEAEs within 30 days post first dose in Season 2 by SOC and PT, there were no clinically meaningful imbalances in favour of any treatment group in the CLD/CHD cohort.

Treatment-emergent NOCDs were reported in one (0.6% [1/180]) subject in the NIRS/NIRS group: nonserious Grade 1 asthma in the CLD cohort on Day 326. This event was not considered to be IP-related.

The incidence of SAEs was numerically higher in the NIRS/NIRS and PALI/NIRS groups than in the PALI/PALI group (12.8% [23/180 subjects] vs 10.0% [4/40 subjects] vs 4.8% [2/42 subjects], respectively). The most common SAEs (≥ 2 subjects) reported in the NIRS/NIRS, PALI/NIRS and PALI/PALI groups were bronchitis viral (3 vs 0 vs 0 subjects), COVID-19 (2 vs 0 vs 0 subjects), gastroenteritis (3 vs 1 vs 1 subjects), LRTI (2 vs 1 vs 0 subjects), pneumonia (2 vs 2 vs 0 subjects), and pleural effusion (2 vs 0 vs 0 subjects), respectively. No clinically relevant imbalances were observed between the treatment groups at the PT level.

Table S2 Overall Summary of Treatment-emergent Adverse Events Through 360 Days Post First Dose in Season 2 – As-treated Population (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)	31 (77.5)	130 (72.2)
Occurring ≤1 day post any dose	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
≥1 event of ≥Grade 3 [b]	2 (4.8)	4 (10.0)	19 (10.6)
Occurring ≤1 day post any dose	0	0	0
Occurring ≤3 days post any dose	0	0	1 (0.6)
Occurring ≤7 days post any dose	0	0	2 (1.1)
Occurring ≤14 days post any dose	0	2 (5.0)	3 (1.7)
≥1 IP-related event of ≥Grade 3 [b]	0	0)	0
Any AE with outcome death	0	0	0
≥1 serious [c] event	2 (4.8)	4 (10.0)	23 (12.8)
≥1 serious [c] or ≥Grade 3 [b] event	3 (7.1)	4 (10.0)	25 (13.9)
≥1 IP-related serious [c] event	0	0	0
≥1 AESI based on investigator assessments	0	0	1 (0.6)
≥1 AESI based on selected MedDRA PT codes	5 (11.9)	5 (12.5)	28 (15.6)
≥1 IP-related AESI based on selected MedDRA PT codes	0	0	0
≥1 IP-related skin reaction	0	0	0
≥1 NOCD	0	0	1 (0.6)
≥1 IP-related NOCD	0	0	0
≥1 event related to COVID-19	7 (16.7)	4 (10.0)	23 (12.8)

Table S2 Overall Summary of Treatment-emergent Adverse Events Through 360 Days Post First Dose in Season 2 – As-treated Population (Season 2)

Subjects [a] with	Number (%) of subjects		
	PALI/PALI (N = 42)	PALI/NIRS (N = 40)	NIRS/NIRS (N = 180)
≥1 confirmed COVID-19 [d]	7 (16.7)	4 (10.0)	20 (11.1)
≥1 suspected COVID-19	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.

[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.

Summary of Pharmacokinetic Results (Season 1 and Season 2)

In both Season 1 and Season 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.

Summary of Pharmacodynamic and RSV Serology Results (Season 1 and Season 2)

Following administration of nirsevimab, subjects in Season 1 had RSV neutralising antibody levels corresponding to a > 115-fold increase from baseline to Day 151 with 98% of subjects having a ≥ 4-fold increase from baseline levels at Day 31. Levels remained higher than baseline levels at Day 361. These high levels of RSV neutralising antibody through Day 361 provide further data supporting protection beyond Day 151.

The RSV neutralising antibody levels following administration of palivizumab were lower than those observed following administration of nirsevimab, consistent with previously reported data showing higher neutralising potency of nirsevimab as compared to palivizumab in nonclinical models of infection.

Following administration of nirsevimab in Season 2, subjects in the NIRS/NIRS and PALI/NIRS groups had RSV neutralising antibody levels corresponding to a > 10-fold and > 157-fold increase from Season 2 baseline to Day 151, respectively. Higher fold-rise in the

PALI/NIRS group corresponded to lower baseline Season 2 concentrations. The RSV neutralising antibody levels for subjects in the NIRS/NIRS and PALI/NIRS groups declined between Days 151 and 361, but remained higher than Season 2 baseline levels.

As expected, both recipients of nirsevimab and palivizumab had measurable pre-F antibody levels post administration. In the Season 1 phase of the study, in subjects who received nirsevimab, GMC of serum antibodies to RSV pre-F antigen increased at Day 31, with > 99% of infants having a ≥ 4-fold rise from baseline, consistent with the mechanism of action of nirsevimab. The pre-F antibody levels declined over time as expected but still remained higher than baseline levels in the nirsevimab group. Geometric mean serum antibodies to RSV post-F antigen levels declined over time in subjects in the nirsevimab group.

In the Season 2 phase of the study, the NIRS/NIRS group had higher peak pre-F antibody levels than either the PALI/NIRS or PALI/PALI groups, whereas the PALI/NIRS and PALI/PALI groups had higher post-F antibody levels than the NIRS/NIRS group, consistent with the different antigenic sites of these monoclonal antibodies (mAbs). Pre-F antibody levels peaked at Day 31 of Season 2 for NIRS/NIRS and PALI/NIRS groups, consistent with the PK results of nirsevimab displayed in Season 1. The PALI/PALI group had peak pre-F and post-F antibody levels at Day 151.

Summary of Immunogenicity Results (Season 1 and Season 2)

In the Season 1 phase of the study, 87.4% (802/918) of the overall study population (ie, all subjects from the preterm and CLD/CHD cohorts) who received study treatment had samples available for ADA assessment at Season 1 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), 77.9% (204/262) of subjects had samples available for ADA assessment at Season 2 Day 361 (144/180 [80.0%] in the NIRS/NIRS group, 36/40 [90.0%] in the PALI/NIRS group, and 24/42 [57.0%] in the PALI/PALI group). The subjects from the preterm cohort did not participate in the Season 2 phase of the study.

Of the subjects who had serum 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 group 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, 5.9% (32/538) of subjects in the nirsevimab group overall, including 6.6% (23/351) of subjects in the preterm cohort and 4.8% (9/187) 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 with those who were negative, revealed no apparent impact of ADA on the safety of nirsevimab through 360 days post first dose of Season 1.

For the 180 CLD/CHD subjects in the NIRS/NIRS group in Season 2 with available serum samples for testing, ADA was detected in 7/174 (4.0%) subjects at Day 361 of Season 1. At Day 31, Day 151, and Day 361 of Season 2, ADA was detected in 1/90 (1.1%), 0/168 (0.0%), and 13/144 (9.0%) subjects, respectively, showing that there was no immune priming in subjects by receipt of a prior nirsevimab dose. Of the 8 subjects with post baseline ADA in Season 1, only one subject had detectable ADA in Season 2, showing that the second nirsevimab dose (Season 2 Day 1) did not boost the immune response.

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 on efficacy could not be evaluated.

Summary of Descriptive Efficacy Results

In the overall population, the incidence of MA RSV LRTI through 150 days post first dose in Season 1 was low and balanced: 0.6% (4/616 subjects) in the nirsevimab group compared with 1.0% (3/309 subjects) in the palivizumab group. The 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 subjects) in the nirsevimab group compared with 0.6% (2/309 subjects) in the palivizumab group. All of these events occurred in the CLD/CHD cohort (1.0% nirsevimab [2/209 subjects], 2.0% palivizumab [2/101 subjects]). For both MA RSV LRTI and MA RSV LRTI with hospitalisation, while the number of events was small, all events in the nirsevimab arm through 150 days post first dose were RSV A. The incidence of All MA LRTI (due to any cause) in Season 1 was also balanced between the treatment groups in the overall population and across the preterm and CLD/CHD cohorts.

In the overall population, there was no incidence of MA RSV LRTI or MA RSV LRTI with hospitalisation through 150 days post first dose in Season 2 in any treatment group. The incidence of All MA LRTI (due to any cause) in Season 2 was low in all 3 treatment groups.

Conclusions

- Nirsevimab had a favourable and comparable safety and tolerability profile to the current standard of care, palivizumab, in the overall population, preterm infants, and those with CLD and/or CHD in Season 1, with similarly favourable and comparable safety and tolerability for subjects with CLD/CHD who received nirsevimab in Season 2.
- Nirsevimab serum concentrations were comparable in preterm and CLD/CHD subjects in Season 1, and similar to those observed in healthy infant studies. Overall, nirsevimab serum concentrations in CLD/CHD subjects were slightly higher in Season 2 than in Season 1.
- The RSV neutralising antibody levels were higher following nirsevimab dosing than palivizumab dosing.
- There is no evidence of immune priming in subjects by receipt of a prior nirsevimab dose and no evidence that the second dose of nirsevimab boosted ADA responses in subjects who had ADA to nirsevimab in Season 1. There was no apparent impact of ADA against nirsevimab 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 on efficacy could not be evaluated.
- In Season 1, incidences of both MA RSV LRTI and MA RSV LRTI with hospitalisation were low and balanced between the treatment groups in the overall population 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.
- 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.