Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials

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Summary

Background In a phase 2b trial and the phase 3 MELODY trial, nirsevimab, an extended half-life, monoclonal antibody against respiratory syncytial virus (RSV), protected healthy infants born preterm or at full term against medically attended RSV lower respiratory tract infection (LRTI). In the MELEDY phase 2–3 trial in infants at higher risk for severe RSV infection, nirsevimab showed a similar safety profile to that of palivizumab. The aim of the current analysis was to assess the efficacy of nirsevimab using a weight-banded dosing regimen in infants born between 29 weeks gestational age and full term.

Methods Infants enrolled in the phase 2b and MELODY trials were randomised (2:1) to receive a single intramuscular injection of nirsevimab (infants weighing <5 kg received 50 mg; those weighing ≥5 kg received 100 mg) or placebo before the RSV season. Infants in MEDLEY were randomised (2:1) to receive one dose of nirsevimab (infants weighing <5 kg received 50 mg; those weighing ≥5 kg received 100 mg) followed by four monthly placebo doses, or five once-a-month intramuscular doses of palivizumab. We report a prespecified pooled efficacy analysis assessing the weight-banded dosing regimen proposed on the basis of the phase 2b and MELODY trials, in addition to extrapolated efficacy in infants with chronic lung disease, congenital heart disease, or extreme preterm birth (<29 weeks' gestational age) based on pharmacokinetic data from the phase 2–3 MEDLEY safety trial. For the pooled efficacy analysis, the primary endpoint was incidence of medically attended RSV LRTI through 150 days post-dose. The secondary efficacy endpoint was number of admissions to hospital for medically attended RSV LRTI. The incidence of very severe RSV LRTI was an exploratory endpoint, defined as cases of hospital admission for medically attended RSV LRTI that required supplemental oxygen or intravenous fluids. We also did a prespecified exploratory analysis of medically attended LRTI of any cause (in the investigator's judgement) and hospital admission for respiratory illness of any cause (defined as any upper respiratory tract infection or LRTI leading to hospital admission). Post hoc exploratory analyses of outpatient visits and antibiotic use were also done. Nirsevimab serum concentrations in MEDLEY were assessed using population pharmacokinetic methods and the pooled data from the phase 2b and MELODY trials. An exposure target was defined on the basis of an exposure–response analysis. To successfully demonstrate extrapolation, more than 80% of infants in MEDLEY had to achieve serum nirsevimab exposures at or above the predicted efficacious target.

Findings Overall, 2350 infants (1564 in the nirsevimab group and 786 in the placebo group) in the phase 2b and MELODY trials were included in the pooled analysis. Nirsevimab showed efficacy versus placebo with respect to the primary endpoint of medically attended RSV LRTI (19 [1%] nirsevimab recipients *vs* 51 [6%] placebo recipients; relative risk reduction [RRR] 79·5% [95% CI 65·9–87·7]). Consistent efficacy was shown for additional endpoints of RSV LRTI hospital admission (nine [1%] nirsevimab recipients *vs* 21 [3%] placebo recipients; 77·3% [50·3–89·7]) and very severe RSV (five [<1%] *vs* 18 [2%]; 86·0% [62·5–94·8]). Nirsevimab recipients had fewer hospital admissions for any-cause respiratory illness (RRR 43·8% [18·8–61·1]), any-cause medically attended LRTI (35·4% [21·5–46·9]), LRTI outpatient visits (41·9% [25·7–54·6]), and antibiotic prescriptions (23·6% [3·8–39·3]). Among infants with chronic lung disease, congenital heart disease, or extreme preterm birth in MEDLEY, nirsevimab serum exposures were similar to those found in the pooled data; exposures were above the target in more than 80% of the overall MEDLEY trial population (94%), including infants with chronic lung disease (94%) or congenital heart disease (80%) and those born extremely preterm (94%).

Interpretation A single dose of nirsevimab protected healthy infants born at term or preterm from medically attended RSV LRTI, associated hospital admission, and severe RSV. Pharmacokinetic data support efficacy extrapolation to infants with chronic lung disease, congenital heart disease, or extreme prematurity. Together, these data suggest that

nirsevimab has the potential to change the landscape of infant RSV disease by reducing a major cause of infant morbidity and the consequent burden on caregivers, clinicians, and health-care providers.

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Introduction

Respiratory syncytial virus (RSV) remains the most common cause of lower respiratory tract infection (LRTI) in infants globally. It is also persistently the most frequent cause of hospitalisation in the first year of life.[1–3] Notably, most hospitalisations due to RSV LRTI occur in otherwise healthy, term infants with no underlying serious comorbidity, for whom there are currently no preventive measures available.[4–6] In addition, RSV can lead to a substantial number of outpatient visits, particularly in the first year of life,[7] compounding the substantial burden on health-care providers and families alike.[8]

Nirsevimab is an anti-RSV monoclonal antibody with an extended half-life in vivo (>3-times longer than a typical monoclonal antibody) that targets the highly conserved epitope site Ø on the prefusion form of the RSV fusion (F) protein.[9] The efficacy of nirsevimab has been assessed in two global, double-blind, randomised, placebo-controlled trials with similar designs: the phase 2b trial (NCT02878330)[10] and the phase 3 MELODY trial (NCT03979313).[11] Both trials met their

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI) is the most frequent cause of hospitalisation during the first year of life worldwide. Although infants born preterm and those with underlying lung or heart disease are among those at highest risk for severe illness, most hospitalisations for RSV LRTI occur in healthy infants born at term. The only existing prophylactic intervention against RSV, palivizumab, is only licensed for use in infants born preterm, those who have chronic lung disease, or those who have congenital heart disease, and requires monthly injections throughout the RSV season to provide sustained protection. We searched ClinicalTrials.gov using the term "respiratory syncytial virus" filtered by "with results", "interventional", and "child (birth-17)" to assess the current RSV prophylactic landscape. Although some new candidates are in development for protection against RSV in infants (including paediatric vaccines, maternal vaccines, and monoclonal antibodies), nirsevimab is currently the most advanced.

Nirsevimab is an anti-RSV monoclonal antibody with an extended half-life in vivo that targets the highly conserved epitope site Ø on the pre-fusion form of the F protein. A single intramuscular injection of nirsevimab has been shown to protect against medically attended RSV LRTI in infants in two pivotal randomised placebo-controlled clinical trials: the phase 2b trial (including infants born at gestational age ≥29 to <35 weeks) and the phase 3 MELODY trial (gestational age ≥35 weeks). In addition, the safety of nirsevimab in infants who were eligible to receive palivizumab prophylaxis under local guidelines has been shown in the phase 2–3 MEDLEY trial.

Added value of this study

Following the phase 2b study of nirsevimab, in which all infants received a fixed dose of 50 mg, pharmacokinetic and drug exposure–response analyses indicated that this dose was suboptimal in infants weighing 5 kg or more. This finding led to the development of the weight-banded dosing regimen of 50 mg for infants <5 kg and 100 mg for infants ≥5 kg, which was subsequently used for the phase 3 MELODY study. In the current Article, we pool data from the phase 2b and MELODY trials to obtain a single point estimate of efficacy for healthy infants born between 29 weeks gestational age and full term, based on this weight-banded dosing that has been approved for clinical use in the EU and UK. Pooling these data provides the most relevant, robust information for the largest and broadest population of healthy infants to date. Consistent efficacy was shown across disease severities: 79·5% against medically attended RSV LRTI, 77·3% against medically attended RSV LRTI requiring hospital admission, and 86·0% against very severe RSV disease. Beyond the direct benefit in disease prevention, there was an associated benefit through the reduction in health-resource use and prescribed antibiotics for any indication. In addition, based on similar pharmacokinetic data, a similar level of efficacy to that found in the pooled analysis is extrapolated to infants with chronic lung disease or congenital heart disease and those with born extremely preterm at less than 29 weeks gestational age.

Implications of all the available evidence

This pooled efficacy analysis demonstrates that a single dose of nirsevimab protects against medically attended RSV LRTI, associated hospital admission, and very severe RSV disease, in healthy infants born at full term or preterm (≥29 weeks gestational age), while also reducing outpatient visits and antibiotic use. In addition, pharmacokinetic data support extrapolation of efficacy to infants with congenital heart disease, chronic lung disease, and extreme preterm birth. Together, these data suggest that nirsevimab has the potential to change the landscape of infant RSV disease by reducing a major cause of infant morbidity and the consequent burden on caregivers, clinicians, and health-care providers.

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primary endpoint, showing statistically significant protection against medically attended RSV LRTI over a 5-month period with nirsevimab use. The phase 2b trial assessed a single, intramuscular, 50-mg dose of nirsevimab administered to healthy preterm infants (gestational age ≥29 to <35 weeks) before the RSV season, and reported a relative risk reduction (RRR) of 70·1% (95% CI 52·3–81·2).[10] On the basis of pharmacokinetic and drug exposure–response analyses, dosing was subsequently optimised to a weight-banded dosing regimen consisting of a single intramuscular dose of 50 mg in infants weighing less than 5 kg and 100 mg in infants weighing 5 kg or more. In the MELODY trial, the RRR using this weight-banded dosing regimen for healthy infants born at term or late preterm (gestational age ≥35 weeks) was 74·5% (49·6–87·1).[11] Additionally, the phase 2–3 MEDLEY trial (NCT03959488) used a palivizumab-controlled study design to assess the safety and pharmacokinetics of nirsevimab administration in infants at increased risk for severe RSV infection, and showed a similar safety profile to that of palivizumab.[12]

The aim of this analysis was to assess the efficacy of nirsevimab using a weight-banded dosing regimen in healthy infants born at term or preterm from 29 weeks gestational age who were included in the phase 2 and 3 trials.[10,11] In addition, we aimed to describe the extrapolation of efficacy on the basis of pharmacokinetic data to infants with chronic lung disease of prematurity, congenital heart disease, or those born extremely preterm (<29 weeks gestational age), who were not represented in the efficacy trials.

Methods

Study design

The current study is a pooled efficacy analysis of nirsevimab based on data from the phase 2b trial and phase 3 MELODY trial, and was prespecified before the trials were conducted. Additionally, we extrapolated the efficacy of nirsevimab in infants at increased risk of severe RSV infection (those with chronic lung disease of prematurity, congenital heart disease, or who were born at <29 weeks gestational age, who were not represented in the efficacy trials) on the basis of pharmacokinetic data from the MEDLEY phase 2–3 trial. All three studies were double-blind, randomised, controlled trials, and study designs have been reported previously.[10–12] The phase 2b trial was conducted at 164 sites across 23 countries in Europe, North America, South America, and Australasia. The MELODY primary cohort was investigated at 160 sites across 21 countries in Europe, North America, and Asia, along with South Africa. MEDLEY was conducted at 126 sites across 25 countries in Europe, North America and Asia, along with South Africa. In all three studies, infants were allocated (2:1) to receive either intramuscular nirsevimab or comparator (placebo or palivizumab) before their first RSV season.

All trials were done in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. Each site had approval from an institutional ethics review board or ethics committee, and appropriate written informed consent was obtained for each infant. Data from the trials were collected by clinical investigators and analysed by ClinChoice (a contract research organisation). Neither the investigators nor the parents or guardians were aware of the trial group assignments.

Participants

The two efficacy trials enrolled distinct populations by gestational age: the phase 2b trial enrolled otherwise healthy infants born preterm (gestational age ≥29 to <35 weeks)[10] and MELODY enrolled healthy infants born at term or late preterm (gestational age ≥35 weeks).[11] Potential participants were excluded from the individual studies if they met national or local criteria to receive palivizumab, had any fever or acute illness within 7 days before randomisation, or had RSV infection before or at the time of randomisation. For the pooled analysis, infants from the phase 2b trial who weighed 5 kg or more at enrolment were excluded because they did not receive 100 mg nirsevimab as required to accord with the weight-banded regimen.

The MEDLEY trial assessed the safety and pharmacokinetics of nirsevimab in infants who were eligible to receive prophylaxis with palivizumab under local guidelines; had chronic lung disease of prematurity warranting therapeutic intervention within the previous 6 months, or had uncorrected, partially corrected, or medically treated congenital heart disease; or were born preterm (≤35 weeks gestational age).[12]

Procedures

Nirsevimab was administered as a single dose of 50 mg in all infants in the phase 2b trial; a single dose of either 50 mg (in infants weighing <5 kg) or 100 mg (in those weighing ≥5 kg) in the MELODY trial; and either a 50-mg dose (in infants weighing <5 kg) or 100-mg dose (in those weighing ≥5 kg), followed by four monthly placebo doses, in the MEDLEY trial. Comparators consisted of placebo in the phase 2b and MELODY trials and palivizumab (five once-per-month doses of 15 mg/kg bodyweight) in the MEDLEY trial.

All infants were followed up through their first RSV season to 150 days post-dose to detect the occurrence of RSV LRTI in any type of medical visit (referred to as medically attended RSV LRTI), including both inpatient and outpatient settings, with use of standardised methodology. The case definition (common for all three studies)[10–12] required detection of RSV on a central test (RT-PCR assay; Lyra RSV plus hMPV, Quidel, San Diego, California, USA), the presence of signs of lower respiratory tract involvement on chest auscultation, and the presence of at least one clinical

sign indicating severe respiratory disease (appendix p 4). All RT-PCR-confirmed RSV isolates obtained from participants who developed medically attended LRTI or were admitted to hospital because of any respiratory illness were subtyped and assessed by genotypic and phenotypic resistance methodologies (appendix p 3).

Blood samples were collected for pharmacokinetic analysis at selected timepoints for at least 150 days post-dose (appendix p 2). All three trials followed up infants for safety assessment for 360 days after post-dose; these results are described elsewhere.[10–12]

Outcomes

The primary efficacy endpoint for the current analysis was medically attended RSV LRTI, according to the aforementioned case definition. The secondary efficacy endpoint was number of hospital admissions for medically attended RSV LRTI. Very severe RSV LRTI, medically attended LRTI of any cause, and admissions to hospital were prespecified exploratory endpoints. Very severe RSV LRTI was defined as hospital admission for medically attended RSV LRTI that required supplemental oxygen or intravenous fluids. A case of medically attended LRTI of any cause included all cases of LRTI in the investigator's judgement. Hospital admission for respiratory illness of any cause was defined as any upper respiratory tract infection or LRTI leading to hospital admission. A prespecified subgroup analysis assessed data by hemisphere, age at randomisation, sex, ancestry or ethnic group, weight at baseline, country, and geographical region. Post hoc exploratory endpoints of health resource use, outpatient visits, and antibiotic use were also assessed.

Pharmacokinetic extrapolation

Extrapolation of efficacy on the basis of pharmacokinetics was planned with the assumption of a similar exposure–response relationship across paediatric populations owing to the mechanism of action of nirsevimab.[13] The pharmacokinetics of nirsevimab were assessed with use of a population pharmacokinetic analysis of pooled data;[10–12,14,15] a nirsevimab exposure target was defined on the basis of an exposure–response analysis of pooled data from the phase 2b trial and MELODY. To successfully demonstrate extrapolation, the proposed weight-banded dosing regimen in the MEDLEY population should result in serum nirsevimab exposures at or above the predicted efficacious target in more than 80% of infants. Individual nirsevimab exposure metrics in infants in MEDLEY were derived from the final population pharmacokinetic model and compared with the nirsevimab exposure target.

Groups of interest in this analysis included those not assessed for efficacy in the phase 2b or MELODY trials but who were included in the MEDLEY study: infants with chronic lung disease, infants with haemodynamically significant congenital heart disease, and infants born extremely preterm (<29 weeks gestational age). Exposure–response analyses on the pooled dataset were done in the as-treated population (all participants who underwent randomisation and received any amount of treatment). The nirsevimab pharmacokinetic target to be used as a surrogate for efficacy, based on an exposure–response analysis of pooled phase 2b and MELODY data and expressed as area under the concentration–time curve

	Placebo group (n=786)	Nirsevimab group (n=1564)
Age, months		
Median (IQR)	2·00 (0·99–3·71)	2·02 (1·00–3·58)
≤3·0	531/786 (68%)	1066/1564 (68%)
>3·0 to ≤6·0	204/786 (26%)	398/1564 (25%)
>6·0	51/786 (6%)	100/1564 (6%)
Sex		
Male	389/786 (49%)	828/1564 (53%)
Female	397/786 (51%)	736/1564 (47%)
Ancestry*		
American Indian or Alaska Native	26/786 (3%)	57/1560 (4%)
Asian	24/786 (3%)	39/1560 (3%)
Black or African American	176/786 (22%)	406/1560 (26%)
Native Hawaiian or other Pacific Islander	8/786 (1%)	12/1560 (1%)
White	478/786 (61%)	919/1560 (59%)
Other	70/786 (9%)	109/1560 (7%)
Multiple categories	4/786 (1%)	18/1560 (1%)
Hemisphere		
Northern	536/786 (68%)	1086/1564 (69%)
Southern	250/786 (32%)	478/1564 (31%)
Weight on day 1, kg		
Median (IQR)	4·35 (3·00–6·00)	4·40 (3·20–6·00)
<5	482/786 (61%)	973/1562 (62%)
≥5	304/786 (39%)	589/1562 (38%)
Gestational age, weeks		
≥29 to ≤32	116/786 (15%)	219/1563 (14%)
>32 to <35	175/786 (22%)	344/1563 (22%)
≥35 to <37	76/786 (10%)	139/1563 (9%)
≥37	419/786 (53%)	861/1563 (55%)
Multiple birth	164/786 (21%)	309/1563 (20%)
Infants per trial		
MELODY	496/786 (63%)	994/1564 (64%)
Phase 2b†	290/786 (37%)	570/1564 (36%)

Data are median (IQR) or n/N (%), based on infants with available data. Data include infants who were dosed according to the proposed weight-banded dosing regimen only (ie, infants weighing <5 kg dosed with 50 mg, and those weighing ≥5 kg dosed with 100 mg). *Ancestry was reported by parents or guardians, and each category (except "multiple categories") comprises infants for whom only that category was selected; "other" comprises infants whose parents or guardians indicated a category other than those listed, and "multiple categories" comprises those for whom more than one category was selected. †Includes only infants who weighed <5 kg at enrolment (ie, those who were treated in accordance with the proposed weight-banded regimen).

Table 1: **Demographics and baseline characteristics (intention-to-treat population)**

	Placebo group (n=786)	Nirsevimab group (n=1564)	Relative risk reduction (95% CI)	p value
Medically attended RSV LRTI*	51 (6%)	19 (1%)	79·5% (65·9–87·7)	<0·0001
Hospital admission for medically attended RSV LRTI†	21 (3%)	9 (1%)	77·3% (50·3–89·7)	0·0002
Very severe RSV LRTI‡	18 (2%)	5 (<1%)	86·0% (62·5–94·8)	<0·0001
Medically attended LRTI of any cause‡§	149 (19%)	191 (12%)	35·4% (21·5–46·9)	<0·0001
Hospital admission for respiratory illness of any cause‡§	51 (6%)	57 (4%)	43·8% (18·8–61·1)	0·0022

Relative risk reduction (95% CI) and p values were estimated on the basis of Poisson regression with robust variance across all case definitions. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus. *The model included study code, treatment group, and stratification factors (age at randomisation and hemisphere) as covariates obtained from PROC MIANALYZE after missing data imputation. †The model included study and treatment group as covariates for pooled studies obtained from PROC MIANALYZE after missing data imputation. ‡The model included treatment as a factor. §Included are all medically attended LRTIs according to the investigator's judgement, regardless of whether they met the clinical criteria for the definition of medically attended LRTI (appendix p 4).

Table 2: **Efficacy of nirsevimab weight-band dose on different case definitions of medically attended LRTI to 150 days post-dose (intention-to-treat population)**

(AUC), was 12·8 days×mg/mL. Further details of the population pharmacokinetic and exposure–response analyses can be found in the appendix (p 2).

See Online for appendix

Statistical analysis

The primary cohort of MELODY, for which the primary efficacy endpoint was previously reported,[11] was pooled according to the assigned treatment regimen with infants from the phase 2b trial who weighed less than 5 kg at enrolment.

Efficacy analyses on the pooled dataset were done in the intention-to-treat population (all participants who were randomly allocated). Analysis of the risk of medically attended RSV LRTI and LRTI of any cause were done with the use of a Poisson regression model with robust variance,[16] including treatment, study, and stratification factors (age group at randomisation [≤3·0, >3·0 to ≤6·0, and >6·0 months] and location [northern or southern hemisphere]) as covariates in the model. Efficacy, presented as RRR (95% CI), was calculated as 1 minus the relative risk estimated from the Poisson model and expressed as a percentage reduction versus placebo. Only the first occurrence of medically attended RSV LRTI in an individual was used in the primary analysis. The SAS PROC GENMOD procedure with the REPEATED statement was used to estimate a robust error variance and avoid overestimation of the error for the estimated relative risk.[16] Multiple imputation was used to impute the event outcome for infants who were not followed up for at least 150 days post-dose and who did not have an RSV-associated LRTI, assuming the observed rate of events in the placebo group and with age at randomisation (a stratification factor) included as a predictor. Imputation was done using the monotone logistic regression method and was repeated 20 times. Inferences from the 20 completed datasets were combined, resulting in the point estimate of log-transformed relative risk and the variance. The secondary endpoint, RSV LRTI requiring hospital admission, and the exploratory endpoints of very severe RSV LRTI and hospital admission due to any cause were analysed similarly to the primary efficacy analysis, but with the stratification factor excluded from the model to avoid convergence issues. These analyses were not adjusted for multiplicity, with the exception of the analysis of the RSV LRTI requiring admission to hospital, which was included in the multiplicity-protected hierarchical testing strategy prespecified for the MELODY trial.

For the prespecified subgroup analysis (hemisphere, age at randomisation, sex, ancestry or ethnic group, weight at baseline, country, and geographical region), the RRRs and corresponding 95% CIs (mid-p adjusted) were estimated on basis of the exact conditional method using PROC GENMOD with no strata.

As a supportive analysis, Kaplan-Meier curves were generated for time to first medically attended RSV LRTI until 150 days post-dose (the origin and start times for the survival analysis were the same, namely the date of dosing). For participants who had the event within 150 days post-dose, the time to event was calculated as follows: date of onset of event−date of dosing+1. Date of onset was defined as the date the infant was first seen by the health-care provider for the corresponding event. For participants who did not have an event within 150 days post-dose, the time to event was censored at the earliest of 151 days, study discontinuation, or last study assessment. The hazard ratio and corresponding 95% CI were obtained from a stratified Cox proportional hazards model with the stratification factors (age at randomisation and hemisphere) as the strata. A visual assessment of the corresponding log (–log) plot was conducted to assess the proportionality of hazards.

The effect of nirsevimab on health resource use, including admissions to hospitals and outpatient visits for LRTI, was explored with descriptive statistics, including exploration of both the magnitude and duration of health resource use, and the need for respiratory support or supplemental oxygen. Throughout the studies, prescriptions of antibiotics were recorded for all indications. The rate of outpatient visits for LRTIs and the number of antibiotic prescriptions over one RSV season were estimated from a Poisson model with robust variance with follow-up time as an offset and adjustment for over-dispersion.

Role of the funding source

AstraZeneca (MedImmune) was involved in the trial design, data collection, data analysis, data interpretation, and writing of the report.

Results

The pooled analysis of infants receiving the weight-banded dose comprised 2350 infants: 860 infants born preterm (≥29 to <35 weeks gestational age) who weighed

less than 5 kg in the phase 2b trial, and 1490 infants born at term or late preterm (≥35 weeks' gestational age) in the primary cohort of the MELODY trial. Overall, 786 infants were allocated to receive placebo and 1564 to receive nirsevimab, median age at randomisation was 2·00 months (IQR 1·00–3·65; range 0·03–11·10), 1133 (48%) infants were female, and 1217 (52%) were male. Demographics and baseline characteristics were similar between nirsevimab and placebo recipients (table 1). 1397 (60%) infants were White, 582 (25%) were Black or African American, 83 (4%) were American Indian or Alaska Native, 63 (3%) were Asian, and 20 (1%) were Native Hawaiian or other Pacific Islander. Although from the phase 2b trial only infants weighing less than 5 kg were included in the analysis (in line with the dosing regimen), the demographics of the two pooled datasets remained similar, with the exception that the median age in infants in the phase 2b trial was 1·60 months (IQR 0·90–2·50), and in MELODY 2·60 months (1·05–4·50; appendix p 5). Overall, 2310 (98%) participants (773 [98%] in the placebo group and 1537 [98%] in the nirsevimab group) completed 151 days of follow-up.

Over a follow-up period of 150 days post-dose, the efficacy (RRR) of a single weight-banded dose of nirsevimab against the primary endpoint of medically attended RSV LRTI was 79·5% (95% CI 65·9–87·7), with 51 (6%) participants in the placebo group and 19 (1%) in the nirsevimab group having an event (table 2). Similar efficacy was found against the secondary efficacy endpoints (reflecting increasing levels of severity), with RRRs of 77·3% (50·3–89·7) against hospital admission for medically attended RSV LRTI (21 [3%] placebo recipients *vs* nine [1%] nirsevimab recipients) and 86·0% (62·5–94·8) against very severe RSV disease (18 [2%] placebo recipients *vs* five [<1%] nirsevimab recipients). Nirsevimab was also associated with an RRR of 35·4% (21·5–46·9) against medically attended LRTI of any cause and 43·8% (18·8–61·1) against hospital admission for respiratory illness of any cause (table 2).

Kaplan-Meier plots of time to first medically attended RSV LRTI (figure 1A) and hospital admission (figure 1B) showed clear divergence between the nirsevimab and placebo curves in the cumulation of events over the entire 150-day post-dose efficacy period, supporting the constancy of the benefit of nirsevimab throughout the typical RSV season (5 months). Visual assessment of the corresponding log (–log) plot for medically attended RSV LRTI to assess the proportionality of hazards indicated that the curves remained parallel, supporting the proportional hazards assumption and thus that the HR is representative over 150 days post-dose (appendix p 9). Consistent efficacy was also observed across subgroups stratified by age at randomisation, sex, ancestry, weight, or geographical region (figure 2).

Although there were no clinically meaningful differences in the frequency of signs of disease severity between treatment groups (appendix p 6), the intensity of treatment required by infants with breakthrough infections was lower in the nirsevimab group than in the placebo group. Of those infants admitted to hospital for RSV LRTI, four (44%) of nine nirsevimab recipients and 17 (81%) of 21 placebo recipients required supplementary oxygen; one (11%) nirsevimab recipient and five (24%) placebo recipients required continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC); and zero nirsevimab recipients and six (29%) placebo recipients were admitted to the intensive care unit (ICU).

Among nirsevimab recipients, 14 (<1%) were infected with RSV A and five (<1%) with RSV B, and among placebo recipients 35 (5%) were infected with RSV A and 16 (2%) with RSV B through 150 days post-dose. Following phenotypic and genotypic analysis, no isolates were identified to be resistant to neutralisation by nirsevimab.

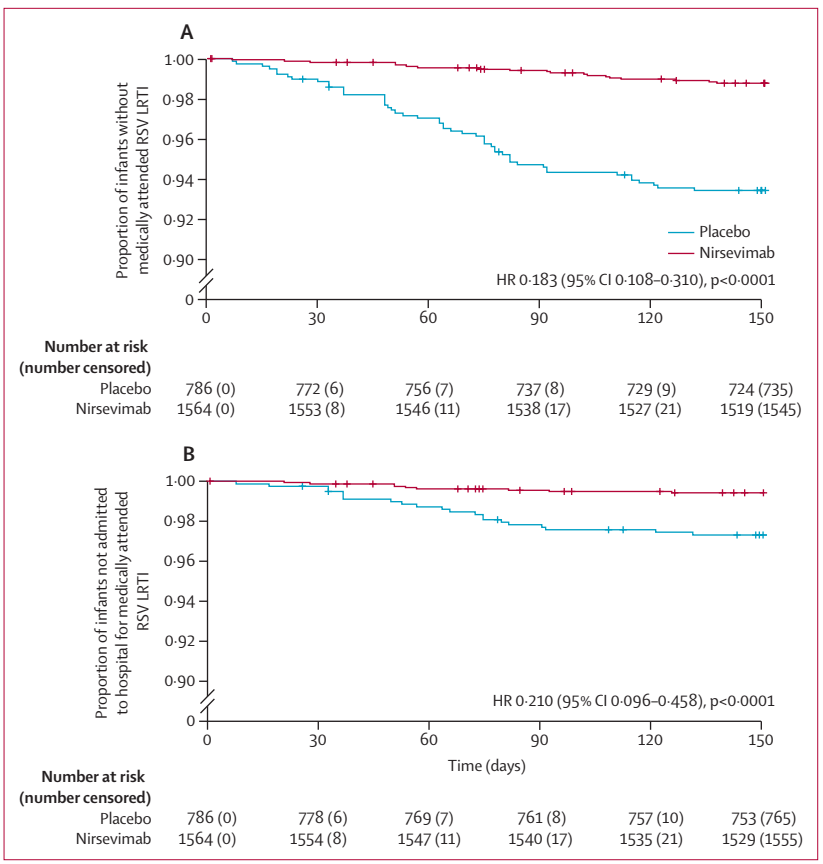

Figure 1: **Kaplan-Meier curves of time to first medically attended RSV LRTI (A) and first hospital admission for medically attended RSV LRTI (B) to 150 days post-dose in the pooled intention-to-treat population**
p values are from stratified log-rank test. HRs are from stratified Cox proportional hazards models. Tick marks indicated censored data. (A) In the analysis of time to first medically attended RSV LRTI, 1545 (99%) of 1564 nirsevimab recipients and 735 (94%) of 786 placebo recipients had no event and were censored; among censored participants, 25 (2%) of 1545 nirsevimab recipients and ten (1%) of 735 placebo recipients were early discontinuations before day 151. (B) In the analysis of time to first hospital admission for medically attended RSV LRTI, 1555 (99%) of 1564 nirsevimab recipients and 765 (97%) of 786 placebo recipients had no event and were censored; among censored participants, 25 (2%) of 1555 nirsevimab recipients and 11 (1%) of 765 placebo recipients were early discontinuations before day 151. HR=hazard ratio. LRTI=lower respiratory tract infection. RSV=respiratory syncytial virus.

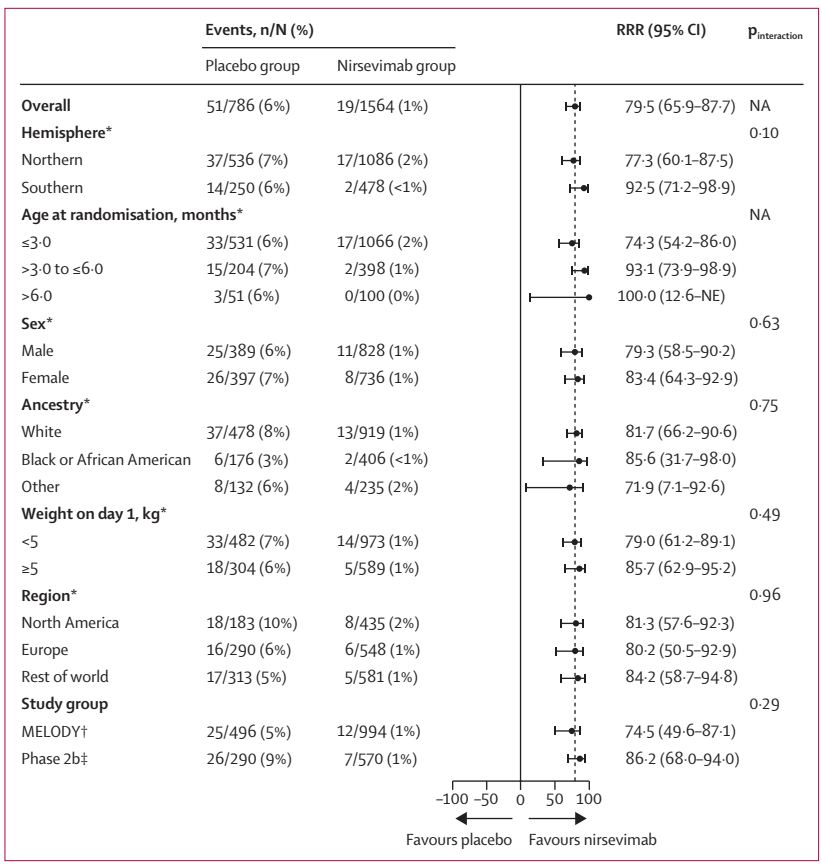

***Figure 2*: Pooled subgroup analyses of medically attended RSV LRTIs through 150 days post-dose (intention-to-treat population)**

The dashed line indicates 80% RRR. LRTI=lower respiratory tract infection. NA=not applicable. NE=not estimable. RRR=relative risk reduction. RSV=respiratory syncytial virus. *RRR and its corresponding 95% CI (mid-p adjusted) were estimated based on an exact conditional method using PROC GENMOD with no strata; $p_{interaction}$ value was obtained from Poisson regression with robust variance, with terms including treatment group, study, age group, hemisphere, subgroup being tested, and treatment-by-subgroup interaction. †RRR, 95% CI, and p value were estimated based on Poisson regression with robust variance, including age at randomisation as a covariate, obtained from PROC MIANALYZE after imputation of missing data. ‡RRR and its corresponding 95% CI were estimated based on stratified Cochran–Mantel–Haenszel test (adjusted for the stratification factors [age at randomisation and hemisphere]).

Infants who received nirsevimab had less frequent outpatient visits for LRTI of any cause and were less frequently prescribed antibiotics for any indication than were infants who received placebo (table 3). Similarly, compared with the placebo group, fewer infants in the nirsevimab group were admitted to hospital for an LRTI of any cause (investigator's judgement), which was reflected in lower mean numbers of days of inpatient health resource use (admitted to hospital, admitted to ICU, or using CPAP or HFNC, mechanical ventilation, or supplemental oxygen) per 100 infants through the RSV season (appendix p 7).

Similar nirsevimab serum concentrations were achieved in MEDLEY as in the MELODY and phase 2b trials of infants weighing less than 5 kg.[10–12] AUCs were above the pharmacokinetic target in more than 80% of the overall MEDLEY trial population (94%) and for all subgroups of special interest: infants with chronic lung disease (94%), infants with haemodynamically significant congenital heart disease (80%), and preterm infants born at less than 29 weeks gestational age (94%; figure 3).

Discussion

In this pooled analysis of two complementary populations of infants entering their first RSV season, a single, prophylactic, intramuscular injection of nirsevimab at 50 mg (for infants weighing <5 kg) or 100 mg (for those weighing ≥5 kg) showed 79·5% efficacy against the primary case definition of medically attended RSV LRTI. Similar efficacy was found for RSV-associated hospital admission and for very severe RSV LRTI requiring supplemental oxygen or intravenous fluids, with substantial protection in infants born preterm or at full term without an underlying risk factor for severe disease. Protection was consistent across geographical areas and by infant age and sex. Adding to the previously published phase 2 and 3 studies of nirsevimab, these pooled data better estimate efficacy in the target population after receipt of a weight-banded dose, and affirm the benefit of nirsevimab in substantially reducing illness and hospital admission in infants.

Given that the mechanism of action of nirsevimab (ie, blockage of entry of RSV at the cellular level) is the same regardless of gestational age at birth, and the similar designs in both studies (including similar enrolment criteria, methods for surveillance, case assessment, and case definitions), pooling of the outcome data is justified. Importantly, this pooled analysis is limited to those infants who received the proposed weight-band dosing regimen, thereby avoiding an underestimate of efficacy that might occur by including the initial dosing strategy used in the phase 2b trial, in which all infants received 50 mg, regardless of their weight.

Overall, consistent efficacy was found across all subgroups and degrees of disease severity. However, some subpopulations had wide 95% CIs along with an RRR of 100%, and these data should therefore be interpreted with caution, although this finding is not unexpected because the studies were not designed to assess efficacy in small subpopulations. Furthermore, although the demonstrable efficacy against all-cause LRTIs does not preclude replacement of RSV by another pathogen, it does provide reassurance that any potential for replacement is outweighed by the overall treatment benefit of nirsevimab against RSV.

Nirsevimab showed activity against both RSV A and RSV B in this pooled analysis, and no isolates resistant to neutralisation by nirsevimab were identified among the breakthrough cases in infants who received the weight-banded dosing regimen. Notably, in the phase 2b trial,[10] two (8%) of 25 infants had an RSV B isolate containing amino acid substitutions associated with nirsevimab resistance; however, these two infants were not included in this pooled analysis because they weighed 5 kg or

	Placebo group (n=786)			Nirsevimab group (n=1564)			Relative risk reduction (95% CI)*
	Number of infants with ≥1 event	Number of events	Number of events per 100 infants (95% CI)	Number of infants with ≥1 event	Number of events	Number of events per 100 infants (95% CI)	
Any antibiotic prescription	157 (20%)	269	34·6 (29·0–41·2)	258 (16%)	409	26·4 (22·8–30·6)	23·6% (3·8–39·3)
Outpatient visits for LRTI	133 (17%)	219	28·1 (23·5–33·8)	171 (11%)	253	16·3 (13·9–19·3)	41·9% (25·7–54·6)

LRTI=lower respiratory tract infection. *Percentage reduction in number of events per 100 infants per RSV season (5 months) in the nirsevimab group versus the placebo group.

***Table* 3: Outpatient visits per LRTI and antibiotic prescription for any cause up to 150 days post-dose (intention-to-treat population)**

more but received only 50 mg nirsevimab, and thus were not dosed in line with the weight-band dosing regimen subsequently developed.

Extrapolation of efficacy on the basis of pharmacokinetics is a common approach to bridging between populations, and has a major role in paediatric drug development,[17] particularly when ethical considerations preclude a placebo-controlled design. Similar to the rationale behind pooling the data from the phase 2b trial and MELODY, this extrapolation relies on the assumptions that the mode of action of nirsevimab and the course of the disease are similar among the populations being assessed. Importantly, nirsevimab pharmacokinetics did not differ substantially in infants with congenital heart disease or chronic lung disease of prematurity; nirsevimab exposures in the MEDLEY subgroups were similar to those in healthy infants born preterm or at full-term, providing support for efficacy in infants with chronic lung disease or congenital heart disease or those born at less than 29 weeks gestational age.

In a previous systematic review, 1·4 million RSV-related hospitalisations and 13 300 in-hospital deaths were estimated to occur worldwide in infants younger than 6 months, accounting for 51% of the total numbers of hospitalisations and deaths in children younger than 5 years.[8] Among infants younger than 2 years, annual rates of RSV-associated visits to the emergency department are estimated to be 59·6 per 1000 children, and to paediatric practice 205·7 per 1000 children.[18] Primary care visits for respiratory diseases have clear, predictable, seasonal patterns, driven primarily by viral circulations,[19] with the frequency of winter visits estimated to be three times higher than that of summer visits at their lowest level, leading to a substantial short-term surge on primary health service demands each winter.[19] Consistent with the findings for other efficacy endpoints,[11] this pooled analysis showed that treatment with nirsevimab lowered the number of outpatient visits for an LRTI of any cause, with numerically fewer infant-days of supplemental oxygen use, respiratory support, and stays in the ICU. Thus, treatment with nirsevimab has the potential to substantially reduce the demand on health-care services and effectively reduce the surge not only in hospitalisations and ICU stays during the winter months but also the outpatient burden, which accounts for more than 90% of RSV disease burden.[7]

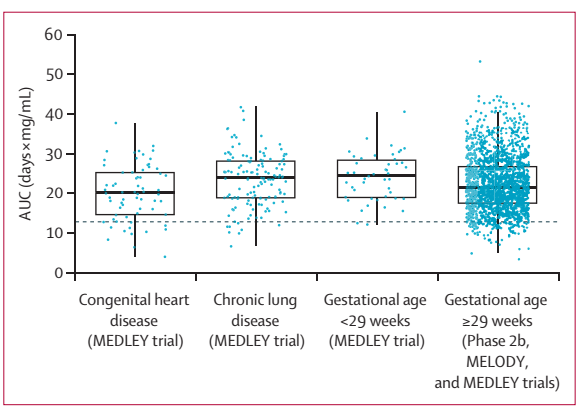

***Figure* 3: Nirsevimab exposures across infant subgroups (as-treated population)**
Points represent individual infants; boxes represent IQRs; central lines correspond to the medians; whiskers extend to the largest and smallest values no further than 1·5 × IQR. The dashed line represents the efficacious target $AUC_{0-\infty}$ of 12·8 day × mg/mL. AUC=area under the concentration–time curve.

Less frequent antibiotic use following receipt of nirsevimab was an unexpected finding. One explanation is a corresponding reduction in secondary bacterial infections known to be associated with RSV infection. RSV infection has been associated with increases in the incidence of otitis media[20] and pneumococcal pneumonia,[21] with up to 40% of children with severe RSV bronchiolitis admitted to ICUs found to have bacterial infection in their lower airways. Moreover, respiratory viruses such as RSV can damage ciliated cells of the airway epithelia, leading to a decline in mucociliary clearance,[22] enhancing the risk of developing a secondary bacterial infection.[23–26] Alternatively, as overprescription of antibiotics remains prevalent in the absence of diagnostic testing,[27,28] and is common in acute respiratory infection,[29] the reduction could be a reflection of fewer infants presenting with RSV LRTI or less severe disease. Indeed, a reduction in antibiotic prescriptions has the potential to beneficially protect the infant microbiome and to reduce the development of antibiotic resistance.[30,31]

A limitation of this analysis is that, although the efficacy of nirsevimab and the difference by treatment group in modalities of health resource use have been

described, it is not possible to generalise the findings to assess the effect on either disease burden or health resource use in the general population, because the proportion of infants born preterm included in this dataset is higher than that in the general population. Thus, the data presented relate only to the included study populations, and analysis of true population-based disease burden reduction and health resource use will depend on future population-based studies.

In conclusion, this pooled analysis of two randomised, placebo-controlled studies showed that prophylaxis with nirsevimab had an efficacy of 79·5% against the primary case definition of medically attended RSV LRTI and was consistent across a range of degrees of severity of RSV LRTI. Efficacy against all-cause medically attended LRTIs and hospital admissions was shown, along with an associated benefit in the reduction in outpatient visits and antibiotic use. On the basis of pharmacokinetic data, a similar degree of efficacy was extrapolated to infants born extremely preterm, those with chronic lung disease, and those with congenital heart disease.

For **AstraZeneca's data sharing policy** see https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

To **request access to study data** see https://vivli.org/

Contributors

SAM, WJM, VA, MB, FC, MBC, JBD, MLG-G, IG, KAM, and HJZ contributed to the investigation and methodology of the study and reviewed and edited the manuscript. EAFS contributed to the investigation and methodology of the study, and wrote the original draft and reviewed and edited subsequent drafts of the manuscript. AB, CC, YY, and UWH contributed to data curation, formal analysis, and validation, and reviewed and edited the manuscript. TT contributed to conceptualisation, investigation, and project administration, and reviewed and edited the manuscript. AL contributed to the conceptualisation, investigation, and methodology of the study, and wrote the original draft and reviewed and edited subsequent drafts of the manuscript. MPG and TV contributed to the conceptualisation, investigation, and methodology of the study, and reviewed and edited the manuscript. All authors had access to the results of the aggregated analysis. EAFS, YY, UWH, and AL accessed and verified the data underlying the study. All authors reviewed the manuscript, were responsible for the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Declaration of interests

EAFS has received grants or contracts from AstraZeneca, Johnson and Johnson, Merck, Pfizer, and Roche; consulting fees from Adiago Therapeutics, Cidara Therapeutics, Merck, Nuance Pharmaceuticals, Pfizer, and Sanofi; payment or honoraria from AstraZeneca and Pfizer; support for meeting attendance and/or travel from AstraZeneca; and has participated in data safety monitoring boards or advisory boards for Abbvie, the Bill and Melinda Gates Foundation, and GSK. SAM has received grants or contracts from the Bill and Melinda Gates Foundation, GSK, Minervax, Pfizer, and the South African Medical Research Council; payments or honoraria from the Bill and Melinda Gates Foundation; and has participated in data safety monitoring boards or advisory boards for PATH and CAPRISA. WJM has received grants or contracts from Ansun, Astellas, AstraZeneca, Eli Lilly, Enanta Pharmaceuticals, Genentech, Gilead, Janssen, Karius, Melinta, Merck, Moderna, Nabriva, Paratek, Pfizer, and Tetraphase; consulting fees from Finley Law Firm and Seqirus; payment or honoraria from Contemporary Pediatrics; and has participated in data safety monitoring boards or advisory boards for Adagio Therapeutics and ProventionBio. FC is a member of the Paediatric Committee at the European Medicines Agency (EMA), but has not participated in the deliberations or decisions related to this product (as communicated to the EMA). JBD has received consulting fees from Sanofi; payment or honoraria from Sanofi; and has participated in data safety monitoring boards or advisory boards for AstraZeneca. HJZ has received grants or contracts from AstraZeneca, MSD, and Pfizer; payment or honoraria from Sanofi; and has participated in data safety monitoring boards or advisory boards for Pfizer. AB, CC, MPG, TT, UWH, AL, and TV are employees of and hold stock or stock options in AstraZeneca. YY is a former employee of and holds stock or stock options in AstraZeneca. All other authors declare no competing interests.

Data sharing

This manuscript has associated data in a repository. Data underlying the findings described in this manuscript, including individual de-identified participant data, protocols, and clinical trial documents, can be obtained in accordance with AstraZeneca's data sharing policy through Vivli.

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