Nirsevimab: Clinical Experience

Study design

Preclinical trials

2014

Phase 1a[1]
NCT02114268
"1st Time in Healthy Adults"

Healthy adults aged 18 to 49 years (n=136)

- N=18 → 300 mg, 1000 mg, or 3000 mg IV nirsevimab
- N=84 → 100 mg or 300 mg IM nirsevimab
- N=34 → Placebo

Evaluation of pharmacokinetics and safety profile of Nirsevimab before initiating a clinical study in infants

Phase 1b/2a[2]
NCT02290340
"1st Time in Healthy Preterm Infants"

Healthy preterm infants 32-35 wGA (n=89)

- N=71 → 10 mg, 25mg or 50 mg IM nirsevimab
- N=18 → Placebo

Evaluation of pharmacokinetics and safety profile of Nirsevimab in healthy preterm infants

Pivotal clinical trials

2016

Phase 2b[3]
NCT02878330
"Infants not eligible to receive Palivizumab as per AAP / other guidelines"

Healthy preterm infants 29-34 weeks 6 days wGA (n=1453)

- N=969 → 50 mg IM nirsevimab
- 2:1
- N=484 → Placebo

Evaluation of nirsevimab for the prevention of RSV-associated lower respiratory tract infection in healthy infants

2019

Phase 3[4,5]
NCT03979313
MELODY STUDY
All

Healthy late preterm and term infants ≥ 35 wGA (n=3012)

- N=2009 → 50 mg or 100 mg IM nirsevimab*
- 2:1
- N=1003 → Placebo

Evaluation of efficacy and safety of nirsevimab in healthy late-preterm and term infants entering their first RSV season

Due to COVID-19, no RSV cases were observed. Therefore, a joint decision with health authorities was taken to analyze the primary endpoint (primary cohort). MELODY trial restarted to further characterize nirsevimab safety in this population (secondary cohort)

2019

Phase 2/3[6-8]
NCT03959488
'MEDLEY'

Preterm cohort (n=615)
2:1 Randomization

Season 1
- N=400 → Single IM dose of nirsevimab (50 mg or 100mg)* → 4 Once monthly doses of placebo
- N=200 → 5 monthly IM doses of palivizumab at 15 mg/kg

Evaluation of safety of nirsevimab in preterm infants with OR without CHD or CLD of prematurity

CHD/CLD cohort (n=310)
2:1 Randomization

- N=200 → Single IM dose of nirsevimab (50 mg or 100mg)* → 4 Once monthly doses of placebo
- N=100 → 5 monthly IM doses of palivizumab at 15 mg/kg

Season 2† (n=262)
- N=200 → Single IM dose of nirsevimab (200 mg) → 4 Once monthly doses of placebo
- 1:1 Randomization
  - N=50 → Single IM dose of nirsevimab (200mg) → 4 Once monthly doses of placebo
  - N=50 → 5 monthly IM doses of palivizumab at 15 mg/kg

2020

Phase 2[9,31]
NCT04484935
'MUSIC'

Immunocompromised children who are ≤ 24 months of age at the time of dose administration. (n=100)

N=42 → **Infants entering 1st RSV season**
Single IM injection of nirsevimab (if <5 kg, 50 mg; if ≥5kg, 100 mg)

N=52 → **Infants entering 2nd RSV season**
Single IM injection of nirsevimab 200 mg

Evaluation of safety and tolerability, for nirsevimab in immunocompromised children

2022

Phase 3b[10]
NCT05437510
'HARMONIE'

Healthy infants ≥29 wGA not eligible for palivizumab (n=8058)

N=4037 → **50 mg or 100 mg IM nirsevimab***
1:1
N=4021 → **No intervention**

Determination of efficacy and safety of nirsevimab for the prevention of hospitalizations due to RSV-LRTI in all palivizumab ineligible infants under 12 months

Key results from the clinical development program of nirsevimab

Safety

Nirsevimab (N=3580): Favorable Safety Profile Across All Infants in pivotal studies

	Ph2b[3] 29-<35 wGA		MELODY[4] ≥35 wGA		MEDLEY First season[6]			
					Preterm		CHD/CLD	
Variables	**Placebo (N=479)**	**Nirsevimab (N=968)**	**Placebo (N=996)**	**Nirsevimab (N=1998)**	**Palivizumab (N=206)**	**Nirsevimab (N=406)**	**Palivizumab (N=98)**	**Nirsevimab (N=208)**
Serious adverse events	16.9%	11.2%	7.4%	6.3%	5.3%	6.9%	20.4%	19.2%
Adverse events of Grade 3 or higher	12.5%	8.0%	3.8%	3.1%	3.4	3.4%	13.3%	14.4%
Adverse events of special interest (AESI)	0.6%	0.5%	0.0%	0.2%	0.0%	0.2%	0.0%	0.5%
Deaths	3	2	0	4	0	2	1	3

- None of the serious adverse events or deaths were considered as related to nirsevimab
- Overall, incidence of nirsevimab antidrug antibody was low across studies with no safety concerns
  - MELODY: Four AESI cases of hypersensitivity limited to cutaneous signs and symptoms
  - MEDLEY: 2 AESIs (nirsevimab arm): Maculopapular rash (preterm cohort) 92 days post nirsevimab dose and heparin-induced thrombocytopenia (CHD/CLD cohort) unrelated to treatment

Clinical experience of nirsevimab continues with HARMONIE, MUSIC, and MELODY

	HARMONIE[10,11]		MUSIC[9]	MEDLEY Second season[12]		
				CHD/CLD		
Variables	**No intervention (N=4020)**	**Nirsevimab (N=4016)**	**Nirsevimab (N=100)**	**P/P (N=42)**	**P/N (N=40)**	**N/N (N=180)**
Serious adverse events	1.7%	2.2%	30%	0%	10%	9.4%
Adverse events of Grade 3 or higher	1.1%	1.2%	31.7	2.4%	10%	7.8%
Adverse events of special interest (AESI)	<0.1	<0.1	6.7%	0%	0%	0%
Deaths	0	0	1	0	0	0

- Overall incidence of adverse events (AEs)[13,14]
  - **Serious AEs and treatment-related AEs were balanced** between Nirsevimab and placebo groups
  - **No anaphylaxis** or other serious allergic reactions
  - **No thrombocytopenia** attributed to study drug
  - **No immune complex disease**
- Nonserious cutaneous **hypersensibility** reactions occurred in **0.2% of nirsevimab recipients**
- Levels of **ADA were low**
- Incidence of **deaths were low and similar between groups**
  - None were considered treatment-related

Key results from the clinical development program

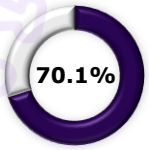
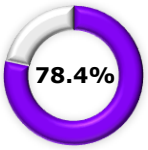
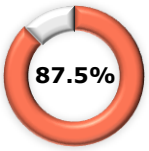
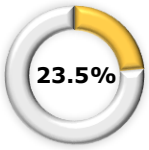
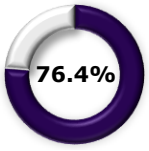
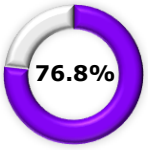
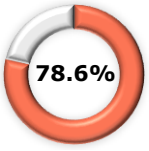
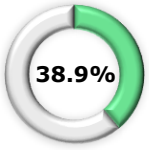
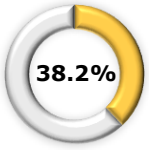
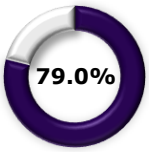
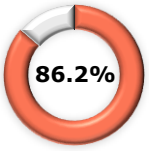
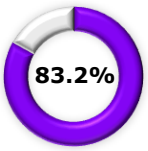
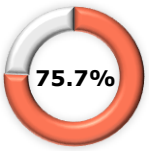
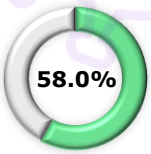
Phase 1a[1]

Nirsevimab administration resulted in a **4X increase** in neutralizing antibodies persisting until day 181 (ranging from 50% in 100 mg IM cohort to 83% in 3000 mg IV cohort)

Phase 1b/2a[2]

The extended half-life and the demonstrated RSV-neutralizing activity supported the potential for protection against RSV disease for the duration of a typical 5-month season with a single 50 mg IM dose of nirsevimab

Consistent efficacy against RSV-LRTI and associated hospitalizations

	RSV MA-LRTI	RSV LRTI Hospitalization	RSV Very severe MA-LRTI	All Cause LRTI Hospitalization	All Cause MA-LRTI
Phase 2b[3,15]	 (95% CI, 52.3-81.2)	 (95% CI, 51.9-90.3)	 (95% CI, 62.9, 95.8)	 (95% CI, 16.3-60.5)	 (95% CI, 7.1-37.0)
MELODY STUDY All[4,5]	 (95% CI, 62.3–85.2)	 (95% CI, 49.4–89.4)	 (95% CI, 48.8–91.0)	 (95% CI, 6.3-60.2)	 (95% CI, 23.7-50.0)
Phase 2b + MELODY STUDY All (Pooled)[5]	 (95% CI, 68.5-86.1)	 (95% CI, 62.3-90.1)	 (95% CI, 68.1-94.0)		
HARMONIE STUDY[10]		 (95% CI, 67.7-92.0)	 (95% CI, 32.8-92.9)	 (95% CI, 39.7-71.2)	

All infants need protection from RSV[16-21].

Nirsevimab is designed to provide protection for all infants for the length of typical RSV season with a single dose[3,22].

Nirsevimab has demonstrated an efficacy of 79% against RSV-MA-LRTI (MELODY/Ph2b pooled), and 83% against hospitalizations (HARMONIE), for 150 days[5,10].

Nirsevimab is the first-in-class and only prevention strategy approved by FDA and EMA and is designed to protect all infants from RSV-LRTI in their first RSV season[23-25].

Regulatory approvals

November 2022	November 2022	April 2023	July 2023
EMA[25]	MHRA[26]	Health Canada[27]	FDA[24]

NITAGs Recommend Nirsevimab for All Infants

Advisory Committee on Immunization Practices[28]

- **First RSV Season**: All infants below 8 months of age
- **Second RSV Season**: Infants and children (8-19 months) at increased risk of severe RSV disease

Haute Autorité de santé[29]

- **First RSV Season**: All infants with reimbursements

Ministerio de Sanidad[30]

- **First RSV Season**: All infants below 6 months of age
- **Second RSV Season**: High risk under 24 months

Abbreviations

AAP: American Academy of Paediatrics; AESI: adverse event of special interest; CHD: Chronic Heart Disease; CLD: Chronic Ling Disease; FDA: Food and Drug Administration; EMA: European Medicines Agency; IM: Intramuscular; IV: Intravenous; LRTI: lower respiratory tract infection; RSV: respiratory syncytial virus; wGA: weeks of gestational age.

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