| **Final Clinical Study Report Synopsis** | |
|---|---|
| Drug Substance | Nirsevimab |
| Study Code | D5290C00008 |
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# A Phase 2, Open-label, Uncontrolled, Single-dose Study to Evaluate the Safety and Tolerability, Pharmacokinetics, and Occurrence of Antidrug Antibody for Nirsevimab in Immunocompromised Children ≤ 24 Months of Age

**Study dates:** First subject enrolled: 19 August 2020.
Last subject last visit: 17 February 2023.
The analysis presented in this report are based on a clinical data lock date of 18 April 2023.

**Phase of development:** Therapeutic exploratory (II)

**International Co-ordinating Investigator:** Not applicable.

**Sponsor's Responsible Medical Officer:** PPD
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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

## Study Centres

One hundred subjects were enrolled and dosed at 28 sites in 8 countries.

## Publications

None at the time of writing this report.

## Objectives and Criteria for Evaluation

**Table S1 Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the safety and tolerability of nirsevimab when administered to immunocompromised children ≤ 24 months of age. | All TEAEs, TESAEs, AESIs, and NOCDs. |
| **Secondary** | |
| To evaluate the PK of nirsevimab. | Summary of nirsevimab serum concentrations. |
| To evaluate ADA responses to nirsevimab in serum. | Incidence of ADA to nirsevimab in serum. |
| To assess the efficacy of nirsevimab when administered as a single IM dose to infants ≤ 24 months of age. | Incidence of MA LRTI (inpatient and outpatient) and hospitalisations due to RT-PCR-confirmed RSV through 150 days after administration of nirsevimab. |
| **Exploratory** | |
| CCI [redacted] | |
| To assess HRU for nirsevimab recipients. | Magnitude of HRU (eg, number of admissions to hospitals and ICUs, and duration of stay; number of subjects who require respiratory support and supplemental oxygen and duration of use; number and type of outpatient visits, eg, ER, urgent care, outpatient clinic; and number of prescription and OTC medications) for nirsevimab recipients. |
| CCI [redacted] | |

[a] CCI [redacted]

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

**Study Design**

This was a Phase II, open-label, uncontrolled, single-dose study to assess the safety and tolerability, pharmacokinetics (PK), occurrence of anti-drug antibodies (ADAs), and descriptive efficacy of nirsevimab in immunocompromised children who were ≤ 24 months of age at time of dose administration.

The study consisted of:

- An Enrolment/Screening Period, which included a Screening Visit (Visit 1) and started 30 days before the Dosing Visit and ended on Day 1.
- A Dosing Visit (Visit 2), where subjects received treatment with the investigational product (IP) nirsevimab.
- A Follow-up Period, which included Visit 3 to Visit 7 and lasted up to Day 361.

**Target Subject Population and Sample Size**

The study was conducted in immunocompromised children ≤ 24 months of age at time of dose administration.

In total, approximately 100 subjects were planned to be enrolled in the study. CCI [redacted]

**Investigational product: Dosage, Mode of Administration, and Batch Numbers**

All subjects received treatment with nirsevimab in this single arm study. The dose received by subjects was dependent upon their age and body weight (at time of dosing):

- Subjects in their first year of life:
  - Subjects with body weight < 5 kg received a single fixed intramuscular (IM) dose of 50 mg nirsevimab.
  - Subjects with body weight ≥ 5 kg received a single fixed IM dose of 100 mg nirsevimab.
- Subjects in their second year of life received a single fixed IM dose of 200 mg (2 × 100 mg) nirsevimab.

The batches of nirsevimab used in the study were A0390A and MEDI-03270.

**Duration of Treatment**

Single dose.

**Statistical Methods**

There were 3 analyses for this study: two interim analyses (IAs) and a final analysis.

- Interim analysis 1 was conducted when all subjects enrolled globally by the end of 2021 had been followed through Day 151. For this IA, all available data (safety, PK, ADA, and descriptive efficacy) at the time of data cut off (16 May 2022) through at least Day 151 were analysed for the 60 subjects enrolled globally in 2021. The results from this IA are reported in the interim clinical study report (iCSR) dated 01 September 2022.
- Interim analysis 2 was conducted when all 100 subjects enrolled had been followed through Day 151. For this IA, all available data (safety, PK, ADA, and descriptive efficacy) at the time of data cut off (19 September 2022) through at least Day 151 were analysed. The results from this IA are reported in the iCSR dated 07 March 2023.
- The final analysis was conducted after all subjects have completed the last visit of the study (ie, Day 361).

No formal statistical comparisons were planned for this study. Data were interpreted through descriptive statistics only. Categorical data were summarised by the number and percentage of subjects. Continuous variables were summarised by mean, median, standard deviation (SD), minimum, and maximum.

Data were summarised for the overall study population (all subjects), as well as for the Japan subpopulation (those subjects enrolled at sites in Japan).

**Study Population**

In total, 106 subjects were screened: 6 (5.7%) subjects were screen failures, and 100 subjects were enrolled and dosed. Overall, 48 subjects received 50 mg or 100 mg nirsevimab and 52 subjects received 200 mg nirsevimab.

The majority of subjects (98 [98.0%] subjects) received the full, planned dose of nirsevimab. Two (2.0%) subjects who were in the second year of life and were planned to receive 200 mg of nirsevimab received 50% of the planned dose (100 mg); these were reported as important protocol deviations (IPDs).

By the end of the study, 6 (6.0%) subjects had discontinued from the study; 3 (3.0%) subjects discontinued due to death (due to lower respiratory tract infection [LRTI], septic shock, and tumour haemorrhage), 1 (1.0%) subject discontinued due to withdrawn consent, 1 (1.0%) subject was lost to follow-up, and 1 (1.0%) subject discontinued due to other reasons (the subject was enrolled in another clinical study and was therefore discontinued from this study by the Investigator). Ninety-four (94.0%) subjects had completed the study.

Ten (10.0%) subjects experienced an IPD, recorded under the categories of laboratory assessments (6 [6.0%] subjects), IP administration (2 [2.0%] subjects), and inclusion/exclusion criteria (2 [2.0%] subjects).

Fourteen (14.0%) subjects missed at least 1 scheduled visit due to the COVID-19 pandemic. All 21 (21.0%) subjects from Ukraine missed at least 1 scheduled visit due to the ongoing Ukraine/Russian conflict.

The majority of subjects were male (65 [65.0%] subjects), either White (45 [45.0%] subjects) or Asian (28 [28.0%] subjects), not Hispanic or Latino (93 [93.0%] subjects). The mean birth weight was 3.20 kg, with 17 (17.0%) subjects ≤ 2.5 kg and 83 (83.0%) subjects > 2.5kg. The mean gestational age a birth was 38.41 weeks. The mean age of subjects at IP administration who received 50 mg/100 mg nirsevimab and who received 200 mg nirsevimab were 7.64 months and 17.90 months, respectively. The mean weight of subjects on Day 1 who received 50 mg/100 mg nirsevimab and who received 200 mg nirsevimab were 7.19 kg and 10.12 kg, respectively.

Subjects could have had more than one immunocompromising condition. Approximately one third of the subjects (33 [33.0%] subjects) met inclusion criterion 2a (diagnosed with primary immunodeficiency); 29 (29.0%) subjects met inclusion criterion 2e (receiving systemic high-dose corticosteroid therapy); 20 (20.0%) subjects met inclusion criterion 2d (receiving immunosuppressive chemotherapy); 16 (16.0%) subjects met inclusion criterion 2c (history of organ or bone marrow transplantation); 15 (15.0%) subjects met inclusion criterion 2f (receiving other immunosuppressive therapy), and 8 (8.0%) subjects met inclusion criterion 2b (diagnosed with HIV).

**Summary of Safety Results**

In total, 81 (81.0%) subjects experienced at least 1 treatment-emergent adverse event (TEAE); the most commonly reported TEAEs were in the system organ classes (SOCs) of Infections and infestations (73 [73.0%] subjects), Skin and subcutaneous tissue disorders (42 [42.0%] subjects), and Gastrointestinal disorders (33 [33.0%] subjects). The most commonly reported TEAEs by preferred term (PT) were upper respiratory tract infection (URTI) (36 [36.0%] subjects), pyrexia (26 [26.0%] subjects), and vomiting (21 [21.0%] subjects).

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

Thirty-two (32.0%) subjects experienced at least 1 treatment-emergent serious adverse event (TESAE), 31 (31.0%) subjects experienced TESAEs of Grade ≥ 3 severity; no TESAEs were considered IP-related, no TESAE was reported in > 5 (5.0%) subjects.

Investigational product-related TEAEs were experienced by 6 (6.0%) subjects, all IP-related TEAEs were of Grade 1 or Grade 2 severity, and all occurred within 7 days of IP administration.

Five (5.0%) subjects experienced adverse events of special interest (AESIs) based on Investigator assessment; all of which were assessed as skin hypersensitivity reactions. None of the AESIs based on Investigator assessment occurred within 1 day of IP administration. A single IP-related AESI occurred during the study (erythema); this was experienced by 1 (1.0%) subject within 3 days of IP administration. There were no serious AESIs reported; all AESIs based on Investigator assessment were of Grade 1 severity.

Adverse events of special interest based on compatible Medical Dictionary for Regulatory Activities (MedDRA) PT codes were identified in 29 (29.0%) subjects; the majority (22 [22.0%] subjects) of whom were subjects with events compatible with PT codes in the hypersensitivity category. Within 1 day of IP administration, 1 (1.0%) subject experienced an IP-related AESI of hypersensitivity based on MedDRA PT codes (rash). The majority of AESIs based on compatible MedDRA PT codes were of Grade 1 or Grade 2 severity. Two (2.0%) subjects experienced 3 AESIs based on MedDRA PT codes of Grade 3 severity (thrombocytopenia); these events were considered TESAEs and unrelated to the IP.

Skin reactions were experienced by 21 (21.0%) subjects; 3 (3.0%) subjects experienced IP-related skin reactions (erythema, rash, and rash maculo-papular; all were of Grade 1 severity). Skin hypersensitivity reactions were experienced by 5 (5.0%) subjects. One (1.0%) subject experienced an IP-related skin hypersensitivity reaction (erythema, Grade 1 severity); the event of erythema was also recorded as an AESI.

There were no events of immune complex disease, anaphylaxis, other severe hypersensitivity, or serious events of thrombocytopenia attributed to the IP in the study.

Clinical laboratory evaluations were performed for the as-treated Japan subpopulation only (N = 26 subjects). Two/26 (7.7%) subjects experienced at least a 2-grade shift from baseline to worst toxicity in white blood cell (leukocyte results); 1/26 (3.8%) subject experienced a shift from Grade 0 to Grade 4, and 1/26 (3.8%) subject experienced a shift from Grade 1 to Grade 3. One/26 (3.8%) subject experienced a 2-grade shift from baseline to worst toxicity (Grade 1 to Grade 3) in aspartate aminotransferase (AST).

One/26 (3.8%) subject experienced a Grade 3 platelet toxicity, 1/26 (3.8%) subject experienced a Grade 3 leukocyte toxicity, and 2/26 (7.7%) subjects experienced a Grade 4

leukocyte toxicity. One/26 (3.8%) subject experienced a Grade 3 AST toxicity, 1/26 (3.8%) subject experienced a Grade 4 alanine aminotransferase (ALT) toxicity. There were no abnormal laboratory results related to the IP, as per Investigator assessment.

No subject who developed treatment-emergent ADAs experienced a skin hypersensitivity reaction, an IP-related skin reaction, or an AESI. One of the ADA-positive subjects experienced an IP-related TEAE (Grade 1 pyrexia within 60 minutes of IP administration) and another ADA-positive subject experienced a skin reaction (Grade 1 rash macular on Day 104) which was not considered related to the IP. Both subjects were ADA-positive on Day 361. There was no apparent impact on the safety results by the presence of ADAs.

**Summary of Pharmacokinetic Results**

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

**Summary of Immunogenicity Results**

Of the 97 subjects with available samples for ADA assessment, 11 (11.3%) subjects developed treatment-emergent ADAs during the study. All 11 (11.3%) subjects were positive for M257Y/S259T/T261E (YTE), and 1 (1.0%) subject was positive for neutralising ADAs.

**Summary of Descriptive Efficacy Results**

None of the medically attended (MA) respiratory syncytial virus (RSV) LRTI met the criteria of a protocol-defined MA RSV LRTI during the study; there were no RSV positive events by either local or central testing reported through 150 days post dose.

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

**Summary of Exploratory Results**

CCI

CCI [redacted]

**Conclusions**

- Nirsevimab demonstrated a favourable safety profile and was well tolerated.
- There were no IP related TEAEs with the outcome of death, IP-related SAEs, IP-related TEAEs of Grade ≥ 3 severity, or NOCD events.
- The IP was well-tolerated in the study population.
- There were no events of immune complex disease, anaphylaxis, other severe hypersensitivity, or serious events of thrombocytopenia related to the IP in the study.
- None of the MA RSV LRTI met the criteria of a protocol defined MA RSV LRTI during the study.
  - There were no RSV positive events by either local or central testing reported through 150 days post dose.
- Nirsevimab serum concentrations were in line with previous studies, with the exception of 14/100 subjects who experienced a more rapid decline in serum concentration over time. The majority of these subjects had evidence of protein-losing conditions (nephrotic syndrome or PLE).
- Anti-drug antibody incidence was 11.3% (11/97 subjects). Based on the available data, the presence of ADAs had no apparent impact on the safety or PK throughout the study, or PK through Day 151.