TechBrief Horizon Scanning	Report No.: 006/2022

MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

NIRSEVIMAB FOR PREVENTION OF RESPIRATORY SYNCYTIAL VIRUS IN INFANTS

EXECUTIVE SUMMARY

Respiratory Syncytial Virus (RSV) is a common respiratory virus that usually causes mild, cold-like symptoms and affects infants and older adults. Current available prophylaxis treatment for RSV needs to be administered five times for one RSV season, which raises the price per season and prevents its best use in low-and middle-income countries. The early evidence of Nirsevimab (*Beyfortus*) prophylaxis treatment showed that it may be efficacious in preventing medically attended RSV-associated lower respiratory tract infection in preterm, late-preterm and term infants. This monoclonal antibody against RSV with an extended half-life, only needs single injection throughout the RSV seasons and thus could help in better compliance, minimising clinic visits and reducing the RSV health care burden. It has been demonstrated to be generally well-tolerated at various doses and comparable with placebo.

Keywords: nirsevimab, MEDI8897, Respiratory Syncytial Virus, infants

INTRODUCTION

Worldwide, RSV significantly increases the morbidity and mortality burden in children aged 0 to 60 months especially during the first 6 months of life and in lower middle income countries.[1] In 2019, it was estimated that there were 6.6 million RSV-associated acute lower respiratory infection episodes (4.6–9.7 million), 1.4 million RSV-associated acute lower respiratory infection hospital admissions (1.0–2.0 million), 13,300 RSV-associated acute lower respiratory infection in hospital deaths (6800–28100), and 45,700 RSV-attributable overall deaths (38,400–55,900) in infants aged 0-6 months.[1] Three additional deaths were

estimated to be attributed to RSV in the community for every death from an acute lower respiratory infection linked with RSV that occurred in a hospital.[1]

In Malaysia, latest preliminary findings from Low et al found that out of 23,000 paediatric patients who presented with acute respiratory infections over five years (2015-2019), 15.9 % (3652/23000) of them were tested positive with RSV.[2] Besides that, it was predominantly detected in children less than 1-year old [p=<0.001, RR=2.05 (95% CI; 1.94 to 2.18)].[2] Children under the age of two were shown to have a considerably higher risk of developing RSV, with rates of 42.3 % for infants under one year old and 42.2 % for those between one and two years old, respectively.[2] The hospitalisations rates due to RSV declined with age and did not cause any hospitalisations in children between the ages of 13 and 17 years old.[2]

In another study conducted on prevalence of viral infections among hospitalised pneumonia patients in equatorial Sarawak found that the most prevalent virus detected was RSV with overall prevalence of 20.4%; prevalence of 26.9% among children <18 years).[3] A total of 85 specimens tested positive by RT-PCR for RSV-A for an overall prevalence of 14.2%.[3]

Therefore, prophylaxis RSV treatment is warranted as it may have a substantial effect on reducing RSV disease burden. The clinical trials of Nirsevimab completed to date have yielded promising results in preventing medically attended RSV-associated lower respiratory tract infection in preterm, late-preterm and term infants.

THE TECHNOLOGY

Nirsevimab (MEDI8897) or Beyfortus is a human recombinant monoclonal antibody designed to provide direct respiratory syncytial virus (RSV) protection to all infants.[4] It is a recombinant human immune globulin G1 kappa monoclonal antibody that binds with the highly conserved site 0 epitope present and lock the RSV protein in the perfusion conformation to block viral entry into the host cell.[5] The nirsevimab antibody is engineered with 3 amino acid changes (M257Y/S259T/T261E [YTE]) in the highly conserved fragment crystallisable region.[4] This YTE modification extends the serum half-life (t1/2) of the antibody beyond the typical 21–28 days.[4] Thus, it may protect infants for an entire RSV season which could translate into durable protection throughout 150 days with a single intramuscular dose.[6] Nirsevimab is being developed and commercialised through a joint agreement between MedImmune (AstraZeneca) and Sanofi.[7]

The U.S. Food and Drug Administration (FDA) has granted breakthrough therapy designation to nirsevimab for the prevention of lower respiratory tract infections caused by RSV, and the European Medicines Agency (EMA) has also granted it access to its PRIority

Medicines (PRIME) scheme for the same indication.[8] Nirsevimab has been recommended for marketing authorisation in the European Union (EU) by the The Committee for Medicinal Products for Human Use (CHMP) of European Medicines Authority based on its positive opinion on results from the nirsevimab clinical development programme, including the MELODY Phase III, MEDLEY Phase II/III, and Phase IIb trials.[9] Furthermore, it has been granted Breakthrough Therapy Designation by The China Center for Drug Evaluation under the National Medical Products Administration and named “a medicine for prioritised development” under the Project for Drug Selection to Promote New Drug Development in Pediatrics by the Japan Agency for Medical Research and Development (AMED).[10]

Nirsevimab is currently on three ongoing studies, including MEDLEY phase 2/3 trials that evaluate the safety of nirsevimab in the preterm infants at risk of severe RSV infection of the lower respiratory tract compared to palivizumab which expected to finish by November 2023. Besides that, there are ongoing phase 2 single-dose study to assess its safety and tolerability, pharmacokinetics, and effectiveness in immunocompromised children who were under 24 months old at the time of dose administration and expected to finish by March,2023. Another trial is currently conducted to assess its safety and effectiveness in healthy preterm and term infants in China (CHIMES). This study is estimated to complete by December, 2025.

PATIENT GROUP AND INDICATION

Nirsevimab is indicated to prevent medically attended RSV-associated lower respiratory tract infection in preterm, late-preterm and term infants. This monoclonal antibody was engineered with modification on its region to extends the serum half-life of the antibody beyond the typical 21–28 days.[4] Thus, it may protect infants for an entire RSV season which could translate into durable protection throughout 150 days with a single intramuscular dose.

According to Centre for Disease Control and Prevention (CDC), respiratory syncytial virus or RSV, is a common respiratory virus that usually causes mild, cold-like symptoms.[11] Most people recover in a week or two, but RSV can be serious, especially for infants and older adults. Respiratory syncytial virus is the most common cause of bronchiolitis (inflammation of the small airways in the lung) and pneumonia (infection of the lungs) in children younger than one year of age.[11]

CURRENT PRACTICE

Currently, palivizumab is the only RSV prophylaxis treatment that is licensed by FDA. It is a monoclonal antibody produced by recombinant DNA technology and sold under the brand name Synagis.[12] It targets the fusion (F) glycoprotein on the surface of RSV, and deactivates it.[12] The F protein is a membrane protein responsible for fusing the virus with its target cell and is highly conserved among subgroups of RSV.[12] Deactivating the F protein prevents the virus from fusing with its target's cell membrane and prevents the virus from entering the host cell.[12] Children age less than two years old and at high risk will be prescribed with the dosage of 15 mg/kg monthly during the RSV season.[12] Subsequent doses should be given monthly until the end of the season.[13] Palivizumab needs to be administered five times for one RSV season, which raises the price per season and prevents its best use in low-and middle-income countries.[13]

EFFICACY AND SAFETY

There were five articles included which were retrieved from the scientific databases (Medline, EMBASE, PubMed), the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] and from the references of retrieved articles. The search was conducted up to 1 September 2022. The five retrieved evidence included three completed clinical trials, one ongoing trials and one disease transmission model study.

The phase 3 randomized, double-blind, placebo-controlled trial called MELODY was conducted to evaluate the safety and efficacy of Nirsevimab before the onset of the RSV season.[14] This study involved 1490 healthy newborns who were born at least 35 weeks' gestational age and were randomly assigned to receive one intramuscular injection of nirsevimab or a placebo.[14] The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection.[14] The secondary efficacy end point was hospitalisations for RSV- associated lower respiratory tract infection through 150 days after the injection.[14] Medically attended RSV-associated lower respiratory tract infection occurred in 12 of 994 infants (1.2%) in the nirsevimab group and in 25 of 496 infants (5.0%) in the placebo group.[14] These findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; $p<0.001$) for nirsevimab.[14]Hospitalisations for RSV-associated lower respiratory tract infection through 150 days after injection occurred in 6 of 994 infants (0.6%) in the nirsevimab group and in 8 of 496 infants (1.6%) in the placebo group (efficacy, 62.1%; 95% CI, −8.6 to 86.8; $p=0.07$).[14] Among infants with data available to day 361, antidrug antibodies after baseline were detected in 58 of 951 (6.1%) in the nirsevimab group and in 5 of 473 (1.1%) in the placebo

group.[14] The types and frequencies of adverse events that occurred during the trial were similar in the two groups.[14] Serious adverse events were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo.[14] Three deaths occurred through day 361 (all among nirsevimab recipients on or after day 140).[14] However, none of the serious adverse events, including the deaths, were considered by the investigators to be related to nirsevimab or placebo.[14] A single adverse event of special interest was reported as one nirsevimab recipient had a grade 3 generalised macular rash without any systemic features six days after the injection, which required no treatment and resolved after 20 days.[14] This trial thus demonstrated that healthy late-preterm and term infants were prevented from medically attended RSV-associated lower respiratory tract infection by a single injection of nirsevimab given prior to the RSV season and generally safe.[14]

In the phase 2b randomised, double-Blind, placebo-controlled trial, nirsevimab was evaluated for the prevention of RSV-associated lower respiratory tract infection in healthy infants who had been born preterm (29 weeks 0 days to 34 weeks 6 days of gestation).[6] This study was conducted with a total of 1453 infants in both northern and southern hemispheres that randomly assigned to receive nirsevimab (969 infants) or placebo (484 infants) at the start of the RSV season.[6] The primary end point was medically attended RSV-associated lower respiratory tract infection through 150 days after administration of the dose.[6] The secondary efficacy end point was hospitalisation for RSV-associated lower respiratory tract infection through 150 days after administration of the dose.[6] Findings show that a single injection of nirsevimab resulted in fewer medically attended RSV-associated lower respiratory tract infections and hospitalisations than placebo through- out the RSV season in healthy preterm infants.[6] Results showed the incidence of medically attended RSV-associated lower respiratory tract infection was 70.1% lower (95% CI, 52.3 to 81.2) with nirsevimab prophylaxis than with placebo (2.6% [25 infants] vs. 9.5% [46 infants]; $p<0.001$) and the incidence of hospitalization for RSV-associated lower respiratory tract infection was 78.4% lower (95% CI, 51.9 to 90.3) with nirsevimab than with placebo (0.8% [8 infants] vs. 4.1% [20 infants]; $p<0.001$).[6] These differences were consistent throughout the 150-day period after the dose was administered and across geographic locations and RSV subtypes.[6] This phase 2b findings indicates that healthy preterm infants receiving a single dose of nirsevimab experienced fewer medically attended RSV-associated lower respiratory tract infections and hospitalisations throughout the RSV season than those receiving a placebo.[6]

The MEDLEY clinical trial is an ongoing phase 2/3 randomised, double-blind, palivizumab-controlled study to evaluate the safety of nirsevimab in the preterm infants at risk for severe

RSV infection of the lower respiratory tract who are eligible to receive palivizumab.[15] This study was conducted to identify the safety and tolerability of nirsevimab, serum concentrations of nirsevimab and palivizumab, incidence of anti-drug antibody and descriptive efficacy of nirsevimab in reducing medically attended LRTI incidence and hospitalization due to RSV.[15] There were 925 preterm infants included (born on or before 35 weeks of gestation) in which 615 of them did not have congenital heart disease (CHD) or chronic lung disease (CLD) of prematurity (preterm cohort) and 310 of the infants who had uncorrected, partially corrected, or medically treated CHD or CLD warranting therapeutic intervention within 6 months (CHD–CLD cohort).[15] Infants were randomly assigned to receive nirsevimab in a single, fixed intramuscular dose of 50 mg if they weighed less than 5 kg and a dose of 100 mg if they weighed 5 kg or more, to be followed by four once-monthly doses of placebo or five once-monthly intramuscular doses of palivizumab (15 mg per kilogram of body weight per dose).[15] Preliminary findings found that incidence of adverse events was similar across treatment groups and cohorts.[15] Seven of the infants receiving nirsevimab had medically attended RSV infections of the lower respiratory tract (4 of 616 infants [0.6%] receiving nirsevimab and 3 of 309 infants [1.0%] receiving palivizumab.[15] At day 151, serum levels of nirsevimab were similar in the two cohorts and similar to those reported in the MELODY trial.[15] The antidrug antibody response at day 151 was low (occurring in 2 of 483 infants [0.4%] in the nirsevimab group and 9 of 251 infants in the palivizumab group [3.6%]).[15] Two adverse events of special interest were reported, both of which occurred in the nirsevimab group: heparin-induced-thrombocytopaenia in an infant with CHD and maculopapular rash following a placebo dose in a preterm infant.[15] Five deaths occurred in the nirsevimab group: two in the preterm cohort and three in the CHD–CLD cohort.[15] One death occurred in the palivizumab group (CHD–CLD cohort). All deaths were unrelated to the treatment.[15]

In a Phase 1b/2a dose-escalation study, target serum concentrations remained above the 90% effective concentration level of 6.8 mg/mL in 87% of infants who received a 50 mg dosage of nirsevimab.[16] A rise in serum RSV-neutralizing antibody levels of about four times from baseline was observed in 90% of healthy preterm infants receiving 50mg dosage.[16] Nirsevimab was also well tolerated at every study doses tested.[16]

The potential impact of nirsevimab on RSV transmission and medically attended lower respiratory tract illness (MALRTI) caused by RSV was conducted by using the disease transmission model with two scenarios either no effect of nirsevimab on transmission in scenario one or 50% reduction of viral shedding in scenario two.[17] This model showed significant benefits increased upon assumption of an effect of nirsevimab on viral shedding. The average reduction of RSV-MALRTIs during RSV epidemic seasons was 49.7%

(~58,000 MALRTIs) among infants aged <6 months and 34.9% (~38,000 MALRTIs) among infants aged 6-12 months.[17] The protection persisted during RSV inter-epidemic seasons, with a reduction of 17.5% (~7300) RSV-MALRTIs among infants <6 months.[17] In second scenario of 50% reduction on viral shedding during the RSV epidemic season, the average reduction of RSV-MALRTIs cases was 51.9% (~61, 000), 36.8% (~40,000) and ranged from 2% for infants aged 0-6 months, 6-12 months, and 12-24 months respectively.[17] This modelling suggests that, compared to no intervention, giving a single dose of nirsevimab to all infants entering or born during their first RSV season may give a considerable benefit.[17]

ESTIMATED COST

There was no retrievable evidence on the exact cost and economic assessment of Nirsevimab. The manufacturers have not announced the treatment's price yet.

Nevertheless, palivizumab may be an alternative to estimate the price range of nirsevimab. The mean cost of palivizumab per dose ranged from $1 661 (MYR 7 408.06; 1 USD =4.46 MYR) for infants younger than six months of age to $2 584 (MYR 11 524.64; 1 USD =4.46 MYR) for children in their second year of life.[18] Immunoprophylaxis with palivizumab cost $302 103 (MYR 1 347 379.38 1 USD =4.46 MYR) for pre-term infants under six months old who had no additional indications.[18] According to Hampp et al, the cost of immunoprophylaxis with palivizumab far exceeded the economic benefit of preventing hospitalisations, even in infants at highest risk for RSV infections.[18] However, another updated cost-effectiveness analysis of palivizumab for the prophylaxis of RSV in United Kingdom infants populations revealed that palivizumab is cost effective in preventing RSV infection requiring hospital admission when used in premature infants born <35 weeks gestational age without congenital heart disease or bronchopulmonary dysplasia aged <6 months at the start of the RSV season, infants aged <24 months with congenital heart disease and infants aged <24 months requiring treatment for bronchopulmonary dysplasia within the last 6 months.[19]

However, in order to compare the cost-effectiveness of nirsevimab in a US birth cohort to the current standard of care, palivizumab, and to no intervention, a static Markov model was developed to estimate RSV-related events and costs in a birth cohort across the first RSV season in the United States.[20] The model predicts 594,596 [537,116 - 617,780] medically attended RSV-LRTIs throughout the course of a season, with an estimated yearly economic cost of $1.3 billion (MYR 579,800,0000; 1 USD =4.46 MYR).[20] Considering a 76% coverage rate and a 70% efficacy, nirsevimab enabled a greater than 50% reduction in the number of

RSV cases.[20] These findings suggest that the most cost-effective approach was to target all infants, where the burden of disease was equally distributed between in-season and out-of-season births due to a seasonal effect and the best implementation approach was seasonal, given the window of protection provided by nirsevimab.[20]

POTENTIAL IMPACT

Respiratory syncytial virus (RSV) is an important public health concern that may cause complication such as bronchiolitis and pneumonia in infants and elderly.[11] Children under the age of two were shown to have a considerably higher risk of developing RSV with higher hospitalisation rates. Current available prophylaxis treatment of RSV called palivizumab needs to be administered monthly for five months until the end of the RSV season.

Nirsevimab offers alternative that may protect infants for an entire RSV season which could translate into durable protection throughout 150 days with a single intramuscular dose. Since only single injection is needed, it could potentially minimising clinic visits, reducing the RSV health care burden and help in better compliance especially in the high risk infants.

However, the ongoing MEDLEY phase 2/3 trials, phase 2 single-dose study in immunocompromised children under 24 months old and CHIMES trial data is needed as further evidence to ascertain the clinical efficacy, safety and cost effectiveness of nirsevimab.

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Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Disclaimer: TechScan report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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