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ADISINSIGHT REPORT

Nirsevimab: First Approval

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Abstract
Nirsevimab (Beyfortus®), a long-acting intramuscular recombinant neutralising human IgG1κ monoclonal antibody to the prefusion conformation of the respiratory syncytial virus (RSV) F protein that has been modified with a triple amino acid substitution in the Fc region to extend the serum half-life, is being jointly developed by AstraZeneca and Sanofi for the prevention of RSV disease. The extended serum half-life allows administration of nirsevimab as a single dose to cover the RSV season. Nirsevimab was approved in the EU on 3 November 2022 and in the UK on 7 November 2022 for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. This article summarizes the milestones in the development of nirsevimab leading to this first approval for the prevention of RSV disease in all infants.

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Nirsevimab (Beyfortus®): Key Points

A long-acting recombinant neutralising human IgG1κ mAb to the prefusion conformation of the RSV F protein being jointly developed by AstraZeneca and Sanofi for the prevention of RSV disease

Received its first approval on 3 November 2022 in the EU

Approved for use in the prevention of RSV LRT disease in neonates and infants during their first RSV season

1 Introduction

Respiratory syncytial virus (RSV) is a common respiratory virus that commonly causes mild, cold-like symptoms in young children. However, in some neonates and infants, RSV can cause serious symptoms and it is the most common cause of lower respiratory tract infections (LRTIs) that can result in hospitalisation or death in this age group [1–3]; approximately 60–80% of infant bronchiolitis and up to 40% of paediatric pneumonia is thought to be due to RSV infection [2]. In 2015, RSV caused an estimated 33.1 million LRTIs worldwide in children aged < 5 years, resulted in hospitalisation in ≈3.2 million of these children and deaths in hospital in ≈ 59,600, most of whom were from low- and middle-income countries. In infants aged < 6 months, acute RSV LRTIs resulted in 1.4 million hospital admissions and 27,300 deaths in hospital [4]. Annual RSV hospitalization rates are highest in infants aged 0-11 months [5]. Palivizumab, an intramuscular (IM) recombinant humanized monoclonal antibody (mAb) that targets the RSV surface fusion glycoprotein (F protein) (developed by AstraZeneca) was approved in 1998 in the USA [6] and then in numerous countries worldwide for the prevention of RSV LRTI infection in specific paediatric patient groups at high risk of RSV disease [7]. While palivizumab is effective in preventing serious RSV LRTIs, administration as five separate doses monthly throughout the RSV season (which typically lasts 5-6 months) because of a shorter half-life ($t_{1/2}$ 20 days) and restriction of the indication to some preterm infants with certain co morbidities only are significant limitations [6–9].

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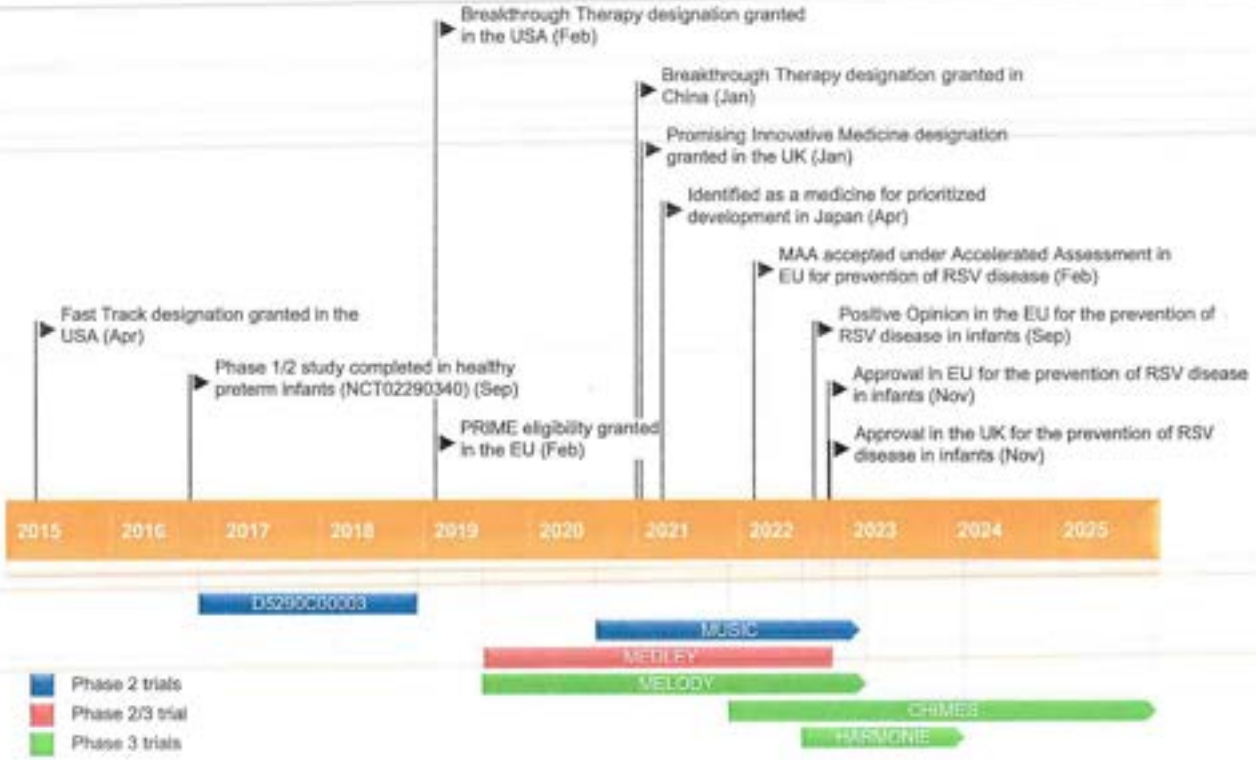

Key milestones in the development of nirsevimab for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season. *MAA* marketing authorization application, *RSV* respiratory syncytial virus

Nirsevimab (Beyfortus®), a long-acting recombinant neutralising human IgG1κ mAb to the prefusion conformation of the RSV F protein that has been modified with a triple amino acid substitution (YTE) in the Fc region to extend the serum half-life, is being jointly developed by AstraZeneca and Sanofi for the prevention of RSV disease. The long serum half-life allows administration of nirsevimab as a single dose to cover the RSV season [10–14]. Nirsevimab was approved in the EU on 3 November 2022 [10–12] and in the UK on 7 November 2022 [13, 14] for the prevention of RSV LRT disease in neonates and infants during their first RSV season.

The recommended dose of nirsevimab is a single dose of 50 mg administered intramuscularly for infants with body weight < 5 kg and a single dose of 100 mg administered intramuscularly for infants with body weight ≥ 5 kg. Nirsevimab should be administered before the RSV season commences or from birth for infants born during the RSV season. [10, 14]. For infants undergoing cardiac surgery with cardiopulmonary bypass, an additional dose may be administered as soon as the infant is stable after surgery to ensure adequate nirsevimab serum levels. If surgery is within 90 days after receiving the first dose of nirsevimab, the additional dose should be 50 mg or 100 mg according to body weight. If more than 90 days have elapsed since the first dose, the additional dose could be a single dose of 50 mg regardless of body weight, to cover the remainder of the RSV season. Dosing in infants with a body weight from 1.0 kg to < 1.6 kg is based on extrapolation (no clinical data are available). Exposures in infants weighing < 1 kg are expected to be higher than in those weighing ≥ 1 kg. There are limited data available in extremely preterm [i.e., gestational age (GA) < 29 weeks)] infants < 8 weeks of age. Nirsevimab can be given concomitantly with childhood vaccines. In clinical trials, when nirsevimab was given with routine childhood vaccines, the safety and reactogenicity profile of the co-administered regimen was similar to the childhood vaccines given alone [10, 14].

1.1 Company Agreements and Patents

In March 2017, AstraZeneca and Sanofi announced an agreement to jointly develop and commercialize nirsevimab for the prevention of RSV infection in neonates and infants [15, 16]. In July 2014, AIMM Therapeutics announced a partnership with AstraZeneca to develop nirsevimab (which originates from the D25 antibody developed by AIMM) for the treatment of RSV infections in young children [17].

In October 2013, AstraZeneca (MedImmune Limited) was granted patent US8562996B2 (RSV-specific binding molecules and means for producing them) [18].

2 Scientific Summary

2.1 Pharmacodynamics

Nirsevimab binds to a highly conserved epitope in antigenic site Ø on the prefusion protein (KD 0.12 nM for RSV subtype A strains and KD 1.22 nM for RSV subtype B strains) locking it in the pre-fusion conformation, unlike palivizumab, which binds to cells expressing the post-fusion RSV-F complex [10, 14]. Nirsevimab neutralises RSV and blocks cell-to-cell fusion by inhibiting the essential membrane fusion step in the viral entry process. [10, 14, 19]. Nirsevimab demonstrated > 50-fold higher activity than palivizumab in vitro and ≈9-fold greater activity than palivizumab against RSV laboratory strains at similar serum concentrations in vivo [19].

Nirsevimab neutralised clinical RSV A and RSV B isolates (70 RSV A and 49 RSV B isolates collected globally in 2013–2017) that encoded the most common RSV F sequence polymorphisms found among circulating strains (median EC_{50} 3.2 ng/mL and 2.9 ng/mL, respectively) in a dose-response model using cultured Hep-2 cells [10, 14, 20]. In vitro, nirsevimab binds to immobilised human FcγRs (FcγRI, FcγRIIA, FcγRIIB and FcγRIII) and shows equivalent neutralising activity compared to parental monoclonal antibodies, IG7 and IG7-TM (Fc region modified to reduce FcR binding and effector function) [10, 14].

Protection from RSV infection is likely to be dependent on nirsevimab neutralisation activity rather than Fc-mediated effector function, based on data from a cotton rat model of RSV infection in which IG7 and IG7-TM exhibited comparable dose-dependent reduction in RSV replication in the lungs and nasal turbinates [10, 14, 19].

To examine antiviral resistance in vitro, escape variants were selected after three passages in cell culture of RSV A2 and B9320 strains in the presence of nirsevimab [10, 14, 20]. Recombinant RSV A variants showing reduced susceptibility to nirsevimab included those with identified substitutions N67I+N208Y (103-fold). Recombinant RSV B variants that showed reduced susceptibility to nirsevimab included those with identified substitutions N208D (> 90,000-fold), N208S (> 24,000-fold), K68N+N201S (> 13,000-fold), or K68N+N208S (> 90,000-fold) [10, 14, 20]. Resistance-associated substitutions identified among neutralisation escape variants were all located in the nirsevimab binding site (amino acids 62-69 and 196-212) and reduced binding affinity to RSV F protein [10, 14, 20].

In the phase 3 MELODY (NCT03979313) and phase 2/3 MEDLEY (NCT03959488) trials, none of the infants with MA RSV LRTI in any treatment group had an RSV isolate containing nirsevimab resistance-associated substitutions [10, 14, 21]. In the phase 2b D5290C00003 trial in which infants were randomized to a single 50 mg dose of nirsevimab (irrespective of weight at time of dosing) or placebo [22], 2 of the 25 infants in the nirsevimab group who had MA RSV LRTI had an RSV isolate containing nirsevimab resistance-associated substitutions (0/11 of those with RSV A and 2/14 of those with RSV B). These recombinant RSV B variants harbouring the identified I64T+K68E+I206M+Q209R (>447.1-fold) or N208S (>386.6-fold) F protein sequence variations in the nirsevimab binding site showed reduced susceptibility to nirsevimab neutralisation. None of the 46 infants in the placebo group who had MA RSV LRTI (24/46 had RSV A and 22/46 had RSV B) had an RSV isolate containing nirsevimab resistance-associated substitution. [10, 14, 22].

In clinical trials, nirsevimab showed activity against recombinant RSV harbouring palivizumab resistance-associated substitutions identified in molecular epidemiology studies, and in neutralisation escape variants of palivizumab. Variants resistant to nirsevimab could possibly have cross-resistance to other mAbs targeting the F protein of RSV [10, 14].

2.2 Pharmacokinetics

Nirsevimab pharmacokinetics were dose-proportional over a dose range 25–300 mg after IM administration of a single dose in clinical trials in infants and adults [10]. C_{max} after IM administration was achieved within 6 days (range 1–28 days) and the estimated bioavailability was 85%. The volume distribution increases with increasing weight. For an infant weighing 5kg, the estimated central and peripheral volume of distribution (V1 and V2) was 249 mL and 241 mL, respectively [10].

Nirsevimab is degraded by proteolytic enzymes and is eliminated by intracellular catabolism [10]. Nirsevimab clearance increases with increased body weight. For an infant weighing 5 kg, the $t_{1/2}$ was ≈69 days [10, 21] and the estimated clearance was 3.38 mL/day [10]. The presence of chronic lung disease or congenital heart disease had no effect on the pharmacokinetics of nirsevimab [10].

On day 151 post administration in the phase 3 MELODY (NCT03979313) trial, mean nirsevimab serum concentrations were 19.6 µg/mL in infants weighing < 5 kg (who had received a 50 mg dose) and 31.2 µg/mL in those weighing ≥ 5 kg (who had received a 100 mg dose) [21]. In the phase 2/3 MEDLEY (NCT03959488) trial in infants at higher risk for severe RSV disease [i.e., extremely preterm infants (gestational age < 29 weeks at birth), and infants with chronic

lung disease (CLD) or congenital heart disease (CHD)], mean serum nirsevimab concentrations in the preterm (n = 401) and CHD/CLD (n = 208) cohorts in infants weighing < 5 kg (who had received a 50 mg dose) were 21.9 µg/mL and 23.9 µg/mL, respectively, and in those weighing ≥ 5 kg (who had received a 100 mg dose) were 34.6 µg/mL and 36.1 µg/mL [23]. In the phase 2b D5290C00003 trial (NCT02878330), serum concentrations in 97.9% (833/851 evaluable) of nirsevimab recipients on day 151 were above the targeted 90% effective concentration threshold of 6.8 µg/mL [22].

Based on pharmacokinetic and clinical data, a single IM dose of nirsevimab provides at least 5 months' protection against RSV LRTI [10]. In the phase 3 MELODY and phase 2b D5290C00003 (NCT02878330) trials of nirsevimab in healthy preterm and term infants, there was a positive correlation between a serum AUC > 12.8 mg·day/mL and a lower incidence of medically attended (MA) RSV LRTI [10]. In the phase 2/3 MEDLEY trial in infants at higher risk for severe RSV disease, > 80% of participants achieved a serum AUC > 12.8 mg·day/mL after a single IM dose of nirsevimab [10]. In the MELODY and D5290C00003 trials, RSV neutralizing antibodies after administration of nirsevimab were ≈ 50-fold higher than baseline at day 151 and ≈ 7-fold higher through day 361 [24].

2.3 Therapeutic Trials

A single IM injection of nirsevimab administered prior to the RSV season prevented MA RSV LRTIs throughout the RSV season in healthy later-preterm (GA ≥ 35 weeks) and term infants aged ≤ 1 year who were entering their first RSV season in the randomized, placebo-controlled phase 3 MELODY trial (NCT03979313) [21]. The incidence of MA RSV LRTIs through 150 days (primary endpoint) in infants administered nirsevimab 50 mg (weight < 5 kg) or 100 mg (weight ≥ 5 kg) [n = 994] was 1.2% compared with 5.0% in those administered placebo (n = 496); this corresponded to an efficacy of 74.5% for nirsevimab ($p < 0.001$ by Poisson regression) and a lower risk of MA RSV LRTI compared with placebo [HR 0.23; 95% CI 0.12–0.47]. There was no significant between-group difference in the incidence of hospitalizations due to RSV LRTI (0.6% vs 1.6%; efficacy for nirsevimab of 62.1%) [10, 21]. The incidence of very severe MA RSV LRTI was 64.2% lower in nirsevimab than placebo recipients (0.5% vs 1.4%) [10]. At baseline, median age was 2.6 months, 86.0% of infants were born at term and 60% weighed ≥ 5 kg. Infants who met local or national criteria to receive palivizumab (i.e., at high risk of RSV disease) were excluded from the trial [21].

Prophylaxis with a single dose of IM nirsevimab significantly reduced the number of MA RSV LRTIs and

Features and properties of nirsevimab

Alternative names	Beyfortus; MEDI8897
Class	Antivirals; Monoclonal antibodies; Recombinant fusion proteins
Mechanism of action	Virus internalisation inhibitors
Route of administration	Intramuscular
Pharmacodynamics	Recombinant neutralising human IgG1κ mAb to the prefusion conformation of the RSV F protein that has been modified with a triple amino acid substitution (YTE) in the Fc region to extend the serum half-life Binds to a highly conserved epitope in antigenic site Ø on the prefusion protein (KD 0.12 nM for RSV subtype A strains and KD 1.22 nM for RSV subtype B strains) > 50-fold higher activity than palivizumab in vitro and ≈ 9-fold greater activity than palivizumab at similar serum concentrations in vivo; neutralised clinical RSV A and RSV B isolates encoding the most common RSV F sequence polymorphisms found among circulating strains in vitro (median EC_{50} 3.2 ng/mL and 2.9 ng/mL)
Pharmacokinetics (after a single IM dose)	Dose-proportional over a dose range 25–300 mg in infants and adults. Cmax ≤ 6 d; estimated absolute bioavailability 85% For a 5 kg infant, estimated V1 249 mL; V2 241 mL; CL 3.38 mL/d; $t_{1/2}$ ≈ 69 d Positive correlation between serum AUC > 12.8 mg·d/mL and lower incidence of MA RSV LRTI
Adverse events	
Most frequent (incidence ≤ 0.7%)	Rash, injection site reaction, pyrexia
ATC codes	
WHO ATC code	J06B-D08 (Nirsevimab)
EphMRA ATC code	J5B5 (Respiratory antivirals excluding influenza products)

hospitalizations throughout the RSV season in healthy preterm (GA ≥ 29 weeks to < 35 weeks) infants aged ≤ 1 year who were entering their first RSV season in the randomized, placebo-controlled phase 2b D5290C00003 trial (NCT02878330) [22]. The incidence of MA RSV RTIs through 150 days (primary endpoint) was 70.1% lower in infants administered nirsevimab 50 mg ($n = 969$) than in those administered placebo ($n = 484$) [2.6% vs 9.5%; $p < 0.001$) [HR 0.26; 95% CI 0.16–0.43] and hospitalizations due to RSV LRTI were reduced by 78.4% (0.8% vs 4.1%; $p < 0.001$) [HR 0.19; 95% CI 0.08–0.44] [10, 22]. The incidence of very severe MA RSV LRTI was 87.5% lower in nirsevimab than placebo recipients (0.4% vs 3.3%) [10]. Infants with a history of CLD/CHD (unless CHD was uncomplicated) were excluded from the trial. At baseline, mean age was 3.3 months, mean body weight was 4.5–4.6 kg, and GA was 32.7 weeks [22].

In a prespecified pooled analysis of data from healthy term and preterm (GA ≥ 29 weeks) infants who received the optimized nirsevimab dosing regimen (i.e., 50 mg in infants < 5kg and 100 mg in infants ≥ 5 kg; $n = 1564$) or placebo ($n = 786$) in MELODY and D5290C00003, RSV LRTI hospitalization through day 150 was 0.6% in the nirsevimab group compared with 2.7% in the placebo group, which corresponded to an efficacy of 77.3% for nirsevimab ($p < 0.001$ by Poisson regression) [21]

In the phase 2/3 MEDLEY (NCT03959488) trial in infants at higher risk for severe RSV disease, the incidence of MA RSV LRTI through 150 days post dose (extrapolated from the efficacy of nirsevimab in MELODY and D5290C00003 based on pharmacokinetic exposure) was 0.6% (4/616) in the nirsevimab group and 1.0% (3/309) in the palivizumab group [10]. MEDLEY, which was primarily a safety and pharmacokinetic study, enrolled extremely preterm infants (GA < 35 weeks; $n = 615$), and infants with CLD or CHD ($n = 310$) entering their first RSV season. Infants were randomized to receive either a single dose of nirsevimab (50 mg in infants < 5kg and 100 mg in infants ≥ 5 kg) followed by four once-monthly doses of placebo or five once-monthly doses of palivizumab 15 mg/kg. Those in the CHD/CLD cohort who underwent cardiac surgery with cardiopulmonary bypass after dose 1 but before dose 5 received a replacement dose of the study drug for dose 1 immediately after surgery [10, 23].

Key clinical trials of nirsevimab

Drug(s)	Indication (patient population)	Phase	Status	Location(s)	Sponsor/collaborator	Identifier
Nirsevimab	Prevention of RSV LRTI (healthy preterm, term infants)	3	Recruiting	France, UK, Germany	Sanofi, AstraZeneca	NCT05437510; HARMONIE; EudraCT2022-000099-20
Nirsevimab, placebo	Prevention of RSV LRTI (healthy preterm, term infants)	3	Recruiting	China	AstraZeneca; Iqvia RDS (Shanghai) Co. Ltd	NCT05110261; CHIMES
Nirsevimab, placebo	Prevention of RSV LRTI (healthy late preterm, term infants)	3	Ongoing	Global	AstraZeneca	NCT03979313; MELODY; EudraCT2019-000114-11
Nirsevimab, palivizumab	Prevention of RSV LRTI (high-risk infants)	2/3	Completed	Global	AstraZeneca	NCT03959488; MEDLEY; EudraCT2019-000201-69
Nirsevimab	Prevention of RSV LRTI (immunocompromised children)	2	Ongoing	Global	AstraZeneca; Iqvia Pty Ltd	NCT04484935; MUSIC; EudraCT2021-003221-30
Nirsevimab, placebo	Prevention of RSV LRTI (healthy preterm infants)	2b	Completed	Global	AstraZeneca	NCT02878330; D5290C00003; EudraCT2016-001677-33

RSV LRTI respiratory syncytial virus lower respiratory tract infection

2.4 Adverse Events

Nirsevimab was well tolerated in clinical trials in infants [10, 14, 21–23]. The most frequent adverse reactions in nirsevimab recipients in pooled data from clinical trials in preterm and term infants (GA ≥ 29 weeks; $n = 1955$) were rash (0.7%; occurring within 14 days of administration; most were mild or moderate in severity), pyrexia (0.6%; occurring within 7 days of administration) and injection site reactions (0.4%; occurring within 7 days of administration; all were non-serious) [10, 14].

In the phase 3 MELODY trial [21] and the phase 2b D5290C00003 trial [22] in healthy preterm and term infants, few participants in the nirsevimab and placebo arms experienced an adverse event considered to be related to the trial regimen (1.0% vs 1.4% [21] and 2.3% vs 2.1% [22], respectively); none of these were considered serious adverse events. No anaphylaxis or other serious hypersensitivity reactions were reported [21, 22]. In the phase 2/3 MEDLEY trial in infants at higher risk of severe RSV disease ($n = 918$ evaluable), the tolerability and safety profile of nirsevimab ($n = 614$) was comparable to that of palivizumab ($n = 304$) and was consistent with that seen in preterm and term nirsevimab recipients in the phase 3 MELODY and phase 2b D5290C00003 trials [10, 14, 23].

Anti-drug antibodies occurring after baseline were detected in 6.1% (58/951 evaluable) of nirsevimab recipients and 1.1% (5/473) of placebo recipients at day 361 in the MELODY trial [21], in 5.6% (52/929) of nirsevimab recipients and 3.8% (18/469) of placebo recipients at day 361 in the D5290C00003 trial [22], and in 0.4% (2/483) of nirsevimab and 3.6% (9/251) of palivizumab recipients at day 151 in the MEDLEY trial [23].

2.5 Ongoing Clinical Trials

In addition to MELODY, ongoing trials of nirsevimab for the prevention of MA RSV LRTI include the phase 2 MUSIC (NCT04484935) trial in immunocompromised infants and children aged ≤ 24 months and two phase 3 trials in healthy preterm and term infants [CHIMES (NCT05110261; conducted in China) and HARMONIE (NCT05437510; conducted in France, the UK and Germany)] that are currently recruiting.

3 Current Status

Nirsevimab received its first approval on 3 November 2022 in the EU [10–12] and on 7 November 2022 in the UK [13, 14] for the prevention of RSV LRT disease in neonates and infants during their first RSV season.

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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