Medicinrådet

Bilag til Medicinrådets vurdering af nirsevimab som forebyggende behandling af RSV-infektion hos spædbørn født til termin

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. nirsevimab som forebyggende behandling af RSV-infektion hos spædbørn født til termin
2. Forhandlingsnotat fra Amgros vedr. nirsevimab som forebyggende behandling af RSV-infektion hos spædbørn født til termin
3. Ansøgers endelige ansøgning vedr. nirsevimab som forebyggende behandling af RSV-infektion hos spædbørn født til termin

Sanofi's svar til Medicinrådets udkast til vurderingsrapport for nirsevimab til forebyggelse af RSV hos spædbørn

Sanofi vil gerne takke Medicinrådet for udkastet til vurderingsrapport. Vi er glade for at se, at Medicinrådet anerkender nirsevimabs overbevisende effekt. Vi anerkender, at der er usikkerhed forbundet med sundhedsøkonomisk modellering i en kompleks sygdom som respiratorisk syncytical virus (RSV) hos spædbørn. Derfor er vi også glade for, at Medicinrådet anerkender, at evalueringer af vacciner typisk fokuserer på bredere samfundsmæssige perspektiver end bare omkostningseffektivitet målt som inkrementelle omkostninger per QALY Ligeledes er vi enige i Medicinrådets fokus på hele årgange af spædbørn, fremfor kun de børn der er født indenfor en RSV-sæson. Kun nirsevimab kan beskytte alle spædbørn, inklusiv præmature og spædbørn født uden for RSV-sæsonen.

Vi har enkelte kommentarer til vurderingsrapporten, som fremgår nedenfor.

Nirsevimab og maternel immuniserings kliniske effekt

Den kliniske effekt af nirsevimab er blevet påvist i adskillige publicerede lodtrækningsforsøg, som inkluderede både tidligt fødte spædbørn og spædbørn født til termin[1-4]. I de inkluderede populationer reducerer nirsevimab antallet af indlæggelser med omkring 80% sammenlignet med placebo eller ingen profylakse. I flere af forsøgene med nirsevimab blev reduktionen i lægetilsete RSV-infektioner vurderet efter fem måneder, hvorfor disse fem måneder indgår som længden af beskyttelsen for nirsevimab - nirsevimab har dog også vist signifikant reduktion af antallet af indlæggelser i perioden 6-12 måneder efter administration[3]. Derudover kan man med nirsevimab immunisere børn, som ikke kan beskyttes med Abrysvo, f.eks. tidligt fødte og tvillinger, ligesom man i Frankrig[5] og USA[6] ikke anbefaler maternel immunisering hos efterfølgende graviditeter hos kvinder, der tidligere er vaccineret.

Effekten af maternel immunisering er derimod kun undersøgt i ét enkelt stort lodtrækningsforsøg blandt kvinder med ukomplicerede singleton-graviditeter[7]. I udkastet til anbefaling lægges der stor vægt på, at maternel immunisering i post-hoc analyser af dette ene studie ser ud til at være mere effektivt, hvis vaccinen gives relativt sent i graviditeten (i eller efter 28. graviditetsuge). Vi anerkender, at der i EMAs 'Public Assessment Report' er data, der understøtter dette, men vil påpege, at disse resultater, som nævnt, kommer fra post-hoc analyser af en subgruppe fra ét enkelt studie, som ikke er publiceret i et peer-reviewedtidsskrift. Data for denne subgruppe findes dog ikke på forebyggelse af RSV-indlæggelser blandt deres spædbørn. Medicinrådet skriver, at effekten på indlæggelser observeret i den fulde population sandsynligvis underestimerer effekten, hvis vaccinen er givet senere i graviditeten. Vi anerkender, at dette muligvis er tilfældet, men vi mener ikke, at Medicinrådets antagelse om, at nirsevimab og Abrysvo har samme kliniske effekt, er velunderbygget.

I den fulde population er effekten af nirsevimab overfor Abrysvo større for indlæggelser end for lægetilsete tilfælde af RSV, med en relativ risiko på 0.583 for lægetilsete infektioner mod 0.456 for hospitalsindlæggelser. Derudover har FDA, som Medicinrådet påpeger, haft adgang til data på hospitalsindlæggelser for spædbørn født af kvinder som er vaccineret mellem 32. og 36. graviditetsuge – her sås en vaccineeffekt på 48,2% (95% CI: -22,9; 79,6), hvilket er sammenligneligt med effektestimatet fra den fulde population (og den øvre grænse for konfidensintervallet er lavere end den observerede effekt af nirsevimab). Vi anser det derfor som overvejende sandsynligt, at selvom Abrysvo muligvis er mere effektivt, hvis vaccinen gives senere i graviditeten, er effekten af nirsevimab stadig større. Endelig ses effekten af maternel immunisering at aftage hurtigt over tid på grund af den lavere halveringstid for maternelle antistoffer. Selvom produktresumeet for Abrysvo angiver, at beskyttelsen varer seks måneder, tyder resultaterne på, at graden af beskyttelse ved seks måneder er lav. I netværksmetaanalysen, som præsenteres i vores ansøgning, benyttedes data fra fem måneder. Da disse estimater bruges i den sundhedsøkonomiske model antages det, at den samme effekt vil gøre sig gældende efter seks måneder; dette er en konservativ antagelse.

Samtidig er det vigtigt at have in mente, at effekten af Abrysvo kun er relevant for spædbørn født tæt på termin og i eller umiddelbart før RSV-sæsonen efter ukomplicerede graviditeter. Nirsevimab forbliver at være den eneste mulighed for at immunisere en hel fødselskohorte.

Erfaringer med nirsevimab fra andre lande

Forebyggelsesprogrammer med nirsevimab er, som nævnt i vurderingsrapporten, blevet implementeret i adskillige europæiske lande med både høj dækningsgrad og store reduktioner i indlæggelser til følge.

Spanien var et af de første lande til at implementere nirsevimab til spædbørn. I Valencia, Murcia og Valladolid sås dækningsgrader varierende fra 78.8% til 98.6%, og effektiviteten af nirsevimab som forebyggelse af hospitalsindlæggelser blev estimeret til 84,4%[8]. I Galicien opnåedes en dækningsgrad på 91,7% og en reduktion i indlæggelser på 82%[9]. Tilsvarende resultater er set i andre spanske regioner[10-14] samt i Frankrig[15,16] og i Luxembourg[17].

Disse resultater viser både, at effekterne fundet i de pivotale studier med nirsevimab også gør sig gældende i en "real-world-setting", og at det er muligt at opnå meget høj tilslutning til et generelt immuniseringsprogram med nirsevimab. Resultater fra real-world studier er ikke tilgængelige for Abrysvo udover de amerikanske effektdata nævnt ovenfor.

I indeværende sæson har også Belgien, Finland, Irland, Italien, Portugal, Schweitz og Tyskland indført programmer med nirsevimab til alle spædbørn.

Dækningsgrad for nirsevimab og maternelle immuniseringsprogrammer

Medicinrådet benytter i deres analyser den samme dækningsgrad for nirsevimab og Abrysvo. Vi vil gerne påpege, at de 80%, som benyttes som dækningsgrad for nirsevimab, er lavere end hvad der er observeret i real-world studier, hvor man på tværs af Europa har opnået dækningsgrader tættere på 90%, og at 80% derfor er et konservativt estimat.

Samtidig har maternelle immuniseringsprogrammer i Danmark historisk set haft relativt lav tilslutning. F.eks. sås tilsutninger på 13% og 27% for Covid-19 og influenza i 2023-sæsonen[18]. Vi anerkender dog, at kighoste-vaccinen, som havde en tilslutning på 70% i 2023-sæsonen[19], kan være en mere relevant sammenligning. I Storbritannien, som er det eneste land i Europa, som har et universelt vaccinationsprogram med maternel immunisering for RSV, har man i 2024-sæsonen opnået en dækningsgrad på omkring 60%, baseret på salgstal og ugentligt forventede graviditeter.

Derfor anser vi de 70% tilslutning, som var antaget i modellen som et højt estimat, og vi mener ikke, at Medicinrådets beslutning om at ændre det til 80% er underbygget af den tilgængelige data.

Mens dækningsgraden for Abrysvo ikke har stor indflydelse på de inkrementelle omkostninger per QALY, har de stor indflydelse på det totale antal undgåede hospitalsindlæggelser. Hvis den reelle tilslutning til et maternelt immuniseringsprogram bliver lavere end anslået i den sundhedsøkonomiske model, vil modellen overvurdere hvor mange hospitalsindlæggelser, der undgåes med Abrysvo.

Administration af nirsevimab

Sanofi har til hensigt at indsende en anmodning om ændring af udleveringstilladelsen for nirsevimab til udleveringsgruppe A. Dette vil betyde, at spædbørn i et eventuelt 'catch-up'-program ikke vil skulle ind på et hospitalsambulatorium, men vil kunne få nirsevimab i primærsektoren.

Dette vil have stor indflydelse på de sundshedsøkonomiske resultater, idet administrationsomkostningerne for nirsevimab til børn født uden for sæson i udkastet til anbefaling er ændret fra 153,50 DKK til 1.989 DKK. Dette er gjort ud fra en antagelse om, at administration ikke sker hos praktiserende læge, men skal foregå i et ambulatorium -som anført ovenfor, forventes det, at nirsevimab vil kunne gives i primærsektoren, som det er tilfældet med palivizumab i dag.

Reduktion af pres på hospitalsafdelinger

Medicinrådet har foretaget flere ændringer af den sundhedsøkonomiske model, som Sanofi ikke er enige i. Vigtigst er, at både dækningsgraden og effektiviteten af nirsevimab og Abrysvo ift. forebyggelse af indlæggelser antages at være den samme.

Selv med disse ændringer vurderer Medicinrådet, at et helårsprogram med catch-up med nirsevimab vil føre til 105 færre indlæggelser end et Abrysvo-program blandt sent præmature og spædbørn født til termin.

Sanofis egen analyse, som er baseret på publiceret data, viser, at et helårsprogram med nirsevimab vil føre til 463 færre indlæggelser end et Abrysvo-program, når der ses på alle spædbørn. Hertil kommer færre besøg hos praktiserende læge, færre henvendelser til pædiatrisk akutmodtagelse, og færre tilfælde af respiratorbehandling.

At et helårsprogram med nirsevimab vil føre til færre indlæggelser skyldes bl.a., at ca. halvdelen af de indlagte med RSV i Europa er født uden for sæson[20-22]. Et Abrysvo-program har svært ved at beskytte denne gruppe, da administration ikke kan times efter sæson.

Baseret på ovenstående mener vi, at det er tydeligt, at nirsevimab er den bedste strategi til at opnå en reel reduktion af presset på pædiatriske hospitalsafdelinger under RSV-sæsoner.

Konklusion

Et program hvor alle spædbørn beskyttes med nirsevimab i deres første RSV-sæson vil føre til den største reduktion i indlæggelser og dermed den største aflastning af hospitalsafdelinger, ligesom et sådant program vil sikre, at alle forældre kan være sikre på, at deres børn har fået den bedst mulige beskyttelse mod alvorlig sygdom.

References

1. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *N Engl J Med* 2023; **389**(26): 2425-35.

2. Simoes EAF, Madhi SA, Muller WJ, et al. 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. *Lancet Child Adolesc Health* 2023; **7**(3): 180-9.

3. Hammitt L, Dagan R, Yuan Y, et al. The Efficacy and Impact in Heathy Infants of Nirsevimab on Medically Attended RSV Lower Respiratory Tract Infection. *Open forum infectious diseases* 2021; **8**(SUPPL 1): S811-S2.

4. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med* 2020; **383**(5): 415-25.

5. Haute Autorité de Santé. Recommandation vaccinale contre les infections à VRS chez les femmes enceintes. 2024.

6. Fleming-Dutra KE, Jones JM, Roper LE, et al. Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus-Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. *MMWR Morb Mortal Wkly Rep* 2023; **72**(41): 1115-22.

7. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023; **388**(16): 1451-64.

8. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. *Eurosurveillance* 2024; **29**(6): 2400046.

9. Ares-Gómez S, Mallah N, María-Isolina S-P, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *Lancet Infectious diseases/˜The œLancet Infectious diseases* 2024.

10. Coma E, Martinez-Marcos M, Hermosilla E, et al. Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalonia (Spain). *Arch Dis Child* 2024; **109**(9): 736-41.

11. Ezpeleta G, Navascues A, Viguria N, et al. Effectiveness of Nirsevimab Immunoprophylaxis Administered at Birth to Prevent Infant Hospitalisation for Respiratory Syncytial Virus Infection: A Population-Based Cohort Study. *Vaccines (Basel)* 2024; **12**(4).

12. Aguera M, Soler-Garcia A, Alejandre C, et al. Nirsevimab immunization's real-world effectiveness in preventing severe bronchiolitis: A test-negative case-control study. *Pediatr Allergy Immunol* 2024; **35**(6): e14175.

13. Barbas Del Buey JF, Inigo Martinez J, Gutierrez Rodriguez MA, et al. The effectiveness of nirsevimab in reducing the burden of disease due to respiratory syncytial virus (RSV) infection over time in the Madrid region (Spain): a prospective population-based cohort study. *Front Public Health* 2024; **12**: 1441786.

14. Estrella-Porter P, Blanco-Calvo C, Lameiras-Azevedo AS, et al. Effectiveness of nirsevimab introduction against respiratory syncytial virus in the Valencian Community: A preliminary assessment. *Vaccine* 2024; **42**(22): 126030.

15. Assad Z, Romain AS, Aupiais C, et al. Nirsevimab and Hospitalization for RSV Bronchiolitis. *N Engl J Med* 2024; **391**(2): 144-54.

16. Paireau J, Durand C, Raimbault S, et al. Nirsevimab Effectiveness Against Cases of Respiratory Syncytial Virus Bronchiolitis Hospitalised in Paediatric Intensive Care Units in France, September 2023-January 2024. *Influenza Other Respir Viruses* 2024; **18**(6): e13311.

17. Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2024; **29**(4).

18. Sundhedsstyrelsen. Erfaringsopsamling - Læringer fra udrulning af

sæsonvaccinationsprogrammer 2022-2023. 2023.

19. Sundhedsstyrelsen, Lægemiddelstyrelsen, Statens Serum Institut. Årsrapport - Børnevaccinationsprogrammet 2023. 2024.

20. Reeves RM, Hardelid P, Panagiotopoulos N, Minaji M, Warburton F, Pebody R. Burden of hospital admissions caused by respiratory syncytial virus (RSV) in infants in England: A data linkage modelling study. *J Infect* 2019; **78**(6): 468-75.

21. Tregoning JS, Schwarze J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. *Clin Microbiol Rev* 2010; **23**(1): 74-98.

22. Drajac C, Laubreton D, Riffault S, Descamps D. Pulmonary Susceptibility of Neonates to Respiratory Syncytial Virus Infection: A Problem of Innate Immunity? *J Immunol Res* 2017; **2017**: 8734504.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

01.12.2025

DBS/HAS

Prisnotat

Dato for behandling i Medicinrådet	17. december 2025
Leverandør	Sanofi
Lægemiddel	Beyfortus (nirsevimab)
Ansøgt indikation	Forebyggelse af respiratorisk syncytialvirus (RSV)-sygdom i nedre luftveje hos nyfødte og spædbørn i løbet af deres første RSV-sæson
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel - udvidet patientpopulation

Prisinformation

[redacted]

Tabel 1 - Listepriser for Beyfortus

Lægemiddel	Styrke	Paknings-størrelse	AIP (DKK)
Beyfortus	50 mg	5 doser pr pakning	30.440,00
Beyfortus	100 mg	5 doser pr pakning	30.440,00

Tabel 2 - Forhandlingsresultat Beyfortus – volumenbaseret aftale

Beyfortus	Interval – antal doser	SAIP pr dosis (DKK)	SAIP pr pakning (DKK)	Rabat ift. AIP
Trin 1*	[redacted]	[redacted]	[redacted]	[redacted]
Trin 2	[redacted]	[redacted]	[redacted]	[redacted]
Trin 3	[redacted]	[redacted]	[redacted]	[redacted]
Trin 4	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Opsummering

[redacted]

Application for the assessment of Beyfortus (nirsevimab) for the prevention of medically attended respiratory syncytial virus in all infants

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[Other]	**[Definition of color-code]**

Contact information

Contact information	
Name	**Birgitte Fyhn**
Company	Sanofi
Title	Head of Market Access and Public Affairs, Denmark
Phone number	+45 24 88 60 32
E-mail	Birgitte.fyhn@sanofi.com
Name (External representation)	**N/A**
Title	
Phone number	N/A
E-mail	

Table of contents

Contact information **2**

Tables and Figures **7**

Abbreviations **11**

1. Regulatory information on the medicine **13**

2. Summary table **14**

3. The patient population, intervention, choice of comparator(s) and relevant outcomes **17**

3.1 The medical condition 17
3.1.1 Virology 18
3.1.2 Pathogenesis 18
3.1.3 Clinical presentation 18
3.1.4 Diagnosis 20
3.1.5 Risk factors 20
3.1.6 Mortality 21
3.1.7 Disease seasonality 21
3.2 Patient population 22
3.3 Current treatment options 22
3.3.1 Prophylaxis with palivizumab 23
3.3.2 Maternal immunisation 23
3.4 The intervention 24
3.4.1 Nirsevimab 24
3.4.2 The intervention in relation to Danish clinical practice 25
3.5 Choice of comparator(s) 25
3.5.1 Standard of care for the prevention of RSV 25
3.5.2 Maternal immunisation 26
3.6 Cost-effectiveness of the comparator(s) 27
3.7 Relevant efficacy outcomes 28
3.7.1 Definition of efficacy outcomes included in the application 28

4. Health economic analysis **29**

4.1 Model structure 30
4.1.1 Subpopulations in the model 31
4.2 Model features 32

5. Overview of literature **33**

5.1 Literature used for the clinical assessment 33
5.2 Literature used for the assessment of health-related quality of life 37

5.3 Literature used for inputs for the health economic model 37

6. Efficacy 41

6.1 Efficacy of nirsevimab versus Abrysvo for prevention of RSV infection in infants 41

6.1.1 Relevant studies 41

6.1.2 Comparability of studies 43

6.1.2.1 Comparability of patients across studies 44

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment 47

6.1.4 Efficacy – results per MELODY 47

6.1.5 Efficacy – results per Griffin et al. 2020 48

6.1.6 Efficacy – results per HARMONIE 48

6.1.7 Efficacy – results per Simoes et al. 2022 49

6.1.8 Efficacy – results per MATISSE 49

6.1.9 Efficacy – Palivizumab 50

6.1.10 Effectiveness – results from real world evidence 51

7. Comparative analyses of efficacy 51

7.1 What is the effect of nirsevimab versus palivizumab in infants who are candidates for palivizumab treatment? 51

7.2 What is the effect of nirsevimab versus placebo in preterm infants (born prior to week 35 of gestational age) 51

7.2.1 Medically attended RSV-associated lower respiratory tract infection 51

7.2.2 RSV-associated hospitalisations 52

7.3 What is the effect of nirsevimab versus placebo in term infants (born after or in week 35 of gestational age) 53

7.3.1 Medically attended RSV-associated lower respiratory tract infection 53

7.3.2 RSV-associated hospitalisations 53

7.4 What is the effect of nirsevimab versus Abrysvo in term infants (born after or in week 35 of gesational age) 54

7.4.1 Differences in definitions of outcomes between studies 54

7.4.2 Method of synthesis 55

7.4.3 Included trials 55

7.4.4 Results from the comparative analysis 56

7.4.5 Efficacy – results per medically attended lower respiratory tract infection caused by respiratory syncytial virus 56

7.4.6 Efficacy – results per RSV-associated hospitalisation 58

7.5 Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation 59

7.6 Efficacy conclusions and interpretation 60

8. Modelling of efficacy in the health economic analysis 61

8.1 Presentation of efficacy data from the clinical documentation used in the model 61

8.1.1 Extrapolation of efficacy data 62
8.1.2 Calculation of transition probabilities 62
8.2 Presentation of efficacy data from [additional documentation] 62
8.3 Modelling effects of subsequent treatments 62
8.4 Other assumptions regarding efficacy in the model 62
8.5 Overview of modelled average treatment length and time in model health state 69

9. Safety 70
9.1 Safety data from the clinical documentation 70
9.2 Safety data from external literature applied in the health economic model 73

10. Documentation of health-related quality of life (HRQoL) 73
10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments] 74
10.1.1 Study design and measuring instrument 74
10.1.2 Data collection 74
10.1.3 HRQoL results 74
10.2 Health state utility values (HSUVs) used in the health economic model 74
10.2.1 HSUV calculation 74
10.2.1.1 Mapping 75
10.2.2 Disutility calculation 75
10.2.3 Mortality-related disutility 76
10.2.4 HSUV results 76
10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy 78
10.3.1 Mao Z. et al. 2022 78
10.3.2 Li X. et al 2022 79
10.3.3 HRQoL Results 79
10.3.4 HSUV and disutility results 79

11. Resource use and associated costs 80
11.1 Medicine costs - intervention and comparator 81
11.2 Medicine costs – co-administration 82
11.3 Administration costs 83
11.4 Disease management costs (RSV specific events) 83
11.5 Costs associated with management of RSV specific complications 85
11.6 Subsequent treatment costs 86
11.7 Patient costs 86
11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) 88

12. Results 89
12.1 Base case overview 89
12.1.1 Base case results 91

12.2 Sensitivity analyses 94
12.2.1 Deterministic sensitivity analyses 94
12.2.2 Scenarios 97
12.2.3 Probabilistic sensitivity analyses 98

13. Budget impact analysis 100
13.1 Number of patients (including assumptions on market share) 100
13.1.1 Market uptake 100
13.2 Budget impact 102

14. List of experts 103

15. References 103

Appendix A. Main characteristics of studies included 111

Appendix B. Efficacy results per study 132

Appendix C. Comparative analysis of efficacy 145
C.1 Methods of synthesis 146
C.1.1 Comparisons against placebo 146
C.1.2 Comparisons against Abrysvo 146

Appendix D. Extrapolation 147

Appendix E. Serious adverse events 148

Appendix F. Health-related quality of life 164

Appendix G. Probabilistic sensitivity analyses 165

Appendix H. Literature searches for the clinical assessment 241
H.1 Efficacy and safety of the intervention and comparator(s) 241
H.1.1 Search strategies 242
H.1.2 Systematic selection of studies 245
H.1.3 Quality assessment 260
H.1.4 Unpublished data 260

Appendix I. Literature searches for health-related quality of life 261
I.1 Objectives 261
I.2 Methods 261
I.2.1 Information sources 261
I.2.2 Search strategies 261
I.2.2.1 Bibliographic database searches 262
I.2.3 Systematic selection of studies 263

I.2.4 Unpublished data 268

Appendix J. Literature searches for input to the health economic model 268

Appendix K. Safety data and patient disposition from MEDLEY 273

Appendix L. Resource use based on RSV-related Health Events 276

L.1.1 Medical resource use 276

L.1.1.1 Inpatient hospitalisation 276

L.1.1.2 Intensive care or observation 277

L.1.1.3 Mechanical ventilation 278

L.1.1.4 Pediatric emergency admission 278

L.1.1.5 Primary care visit 279

Appendix M. PSA results by subgroup 280

M.1 Palivizumab eligible population 280

M.1.1 Nirsevimab vs Maternal immunisation 280

M.1.2 Nirsevimab vs SoC 281

M.2 Preterm infant population 281

M.2.1 Nirsevimab vs Maternal immunisation 281

M.2.2 Nirsevimab vs SoC 282

M.3 Term infant population 282

M.3.1 Nirsevimab vs Maternal immunisation 282

M.3.2 Nirsevimab vs SoC 283

Tables and Figures

Table 1 Incidence and prevalence of lab-confirmed RSV in the past 5 years 22

Table 2 Estimated number of infants eligible for treatment (population projections) 22

Table 3 Efficacy outcome measures relevant for the application 28

Table 4 Model features 32

Table 5 Relevant literature included in the assessment of efficacy and safety 35

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 0) 37

Table 7 Relevant literature used for input to the health economic model 38

Table 8 Overview of study design for studies included in the comparison 42

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety 44

Table 10 Characteristics in the relevant Danish population and in the health economic model 47

Table 11. Efficacy results from MELODY (All subjects) 47

Table 12. Efficacy results from Griffin et al. 2020 48

Table 13. Efficacy results from HARMONIE 48

Table 14. Efficacy outcomes from Simoes et al. 2022 49

Table 15. Efficacy results from MATISSE 49
Table 16. Trials included in the meta-analysis for RSV-associated hospitalisation (<35 wGA) 52
Table 17. Trials included in the meta-analysis for RSV-associated hospitalisation (>=35 wGA) 54
Table 18. Definitions of outcomes included in the comparative analysis of nirsevimab versus Abrysvo 54
Table 19. Trials included in the network meta-analysis for RSV-associated hospitalisation 55
Table 20. Trials included in the network meta-analysis for RSV-associated hospitalisation 56
Table 21 Results from the random effects NMA of nirsevimab vs. Abrysvo for prevention of RSV in infants 56
Table 22. Absolute effect estimates obtained from the NMA of RSV MA-LRTI 57
Table 23. Absolute effect estimates obtained from the NMA of RSV hospitalisations 58
Table 24. Adverse health events under each scenario and number of prevented events with nirsevimab relative to SoC and Abrysvo – from the health economic model, base case settings. 61
Table 25 Summary of assumptions associated with extrapolation of [effect measure] 62
Table 26 Transitions in the health economic model 62
Table 27. Assumptions and inputs used in the base case in the health economic model 63
Table 28 All-cause mortality 68
Table 29 Estimates in the model 69
Table 30 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) 69
Table 31 Overview of safety events in studies included in the NMA. 70
Table 32 Serious adverse events 73
Table 33 Adverse events used in the health economic model 73
Table 34 Adverse events that appear in more than X % of patients 73
Table 35 Overview of included HRQoL instruments 74
Table 36 Pattern of missing data and completion 74
Table 37 HRQoL [instrument 1] summary statistics 74
Table 38 Overview of RSV related disutilities 77
Table 39 Total utility loss per premature death 77
Table 40 Overview of health state utility values [and disutilities] 79
Table 41 Overview of literature-based health state utility value 79
Table 42 Prophylaxis dosing and frequency used in the model 81
Table 43 Prophylaxis costs used in the model 82
Table 44 additional visits related to intervention and comparators 83
Table 45 Administration costs used in the model 83
Table 46 Health event settings in the models 83
Table 47 RSV management costs used in the models 84

Table 48 Inpatient hospitalisations, ICU (incl. hospitalisation), and MV by GA 85
Table 49 Complications settings in the models 85
Table 50 Cost associated with management of RSV complications 86
Table 51 Patient time assumptions, per visit 87
Table 52 Patient costs used in the model, per visit 88
Table 53 Base case overview – Model 1 (maternal immunisation) 89
Table 54 Base case overview – Model 2 (SoC) 90
Table 55 Base case results, discounted estimates 92
Table 56 One-way sensitivity analyses results – Model 1 (maternal immunisation) 94
Table 57 One-way sensitivity analyses results – Model 2 (SoC) 95
Table 58 Scenarios results – Model 1 (maternal immunisation) 97
Table 59 Scenarios results – Model 2 (SoC) 98
Table 60 Percentage of total births, by subgroup 100
Table 61 Number of new patients expected to be treated over the next five-year period if nirsevimab is introduced (adjusted for market share) – against maternal immunisation 101
Table 62 Number of new patients expected to be treated over the next five-year period if nirsevimab is introduced (adjusted for market share) – against SoC 101
Table 63 Expected budget impact of recommending nirsevimab against maternal immunisation 102
Table 64 Expected budget impact of recommending nirsevimab against SoC 103
Table 65 Main characteristic of studies included - MELODY 111
Table 66. Main characteristics of studies included – Griffin et al. 2020 113
Table 67. Main characteristics of studies included - HARMONIE 115
Table 68. Main characteristics of included studies - MEDLEY 119
Table 69. Main characteristics of included studies - Simoes et al. 2022 122
Table 70. Main characteristics of included studies - MATISSE 126
Table 71 Results per MELODY 132
Table 72. Results per Griffin et al. 2020 134
Table 73. Results per HARMONIE 136
Table 74. Results per Simoes et al. 2022 138
Table 75. Results per MATISSE 140
Table 76. Design, population and outcomes of studies included in frequentist NMA 145
Table 77. Serious adverse events observed in MELODY 148
Table 78. Serious adverse events observed in Griffin et al. 2020 151
Table 79. All serious adverse events observed in HARMONIE 154
Table 80. All serious adverse events observed in MEDLEY 156
Table 81. All serious adverse events observed in Simoes et al. 2022 160
Table 82. All serious adverse events observed in MATISSE 162
Table 83. Overview of parameters in the PSA (Model 1) 165
Table 84 Overview of parameters in the PSA (Model 2) 203
Table 85 Bibliographic databases included in the literature search 242
Table 86 Other sources included in the literature search 242
Table 87 Search strategy for Embase (OVID, February 12th, 2024) 242
Table 88. Search strategy for MEDLINE (OVID, February 12th, 2024) 243

Table 89. Search strategy for CENTRAL (Cochrane Library, February 12th, 2024) 244
Table 90. Search strategy for Clinicaltrials.gov (https://clinicaltrials.gov, February 22nd, 2024) 245
Table 91. Search strategy for EUCTR (https://clinicaltrialsregister.eu, February 22nd, 2024) 245
Table 92. Inclusion and exclusion criteria used for assessment of studies 245
Table 93. Studies identified in broad SLR, not included in submission 248
Table 94. Studies from the broad SLR, included in the submission 250
Table 95. Records excluded at full-text screening stage 255
Table 96. Bibliographic databases included in the literature search 261
Table 97. Search strategy - MEDLINE (Pubmed - 10/07/2024) 262
Table 98. Search strategy - MEDLINE (Embase - 10/07/2024) 262
Table 99. Inclusion and exclusion criteria used for assessment of studies 263
Table 100 Overview of excluded studies 264
Table 101 Overview of relevant studies for the SLR 267
Table 102. Search strategy - Input to the health economic model - MEDLINE (06-09-2024) 268
Table 103. Studies excluded after full text screening (literature for the health economic model) 270
Table 104. Safety data – MEDLEY (Season 1) 273
Table 105. RSV-related health events – hospitalisations 276
Table 106. RSV-related health events –Intensive care or observation 277
Table 107. RSV-related health events – MV 278
Table 108. RSV-related health events – pediatric emergency admission 278
Table 109. RSV-related health events – PC visit 279

Figure 1 Disease seasonality in Denmark (0-5 months of age) 21
Figure 2 Model structure 30
Figure 3. Forest plot for meta-analysis of palivizumab versus placebo - RSV Hospitalisation 50
Figure 4. Results from Griffin et al. 2020 for the outcome of RSV MA-LRTIs (150 days post-randomisation) 52
Figure 5. Results of meta-analysis of nirsevimab versus placebo for the outcome of RSV MA-LRTIs (150 days post-randomisation, <35 wGA) 53
Figure 6. Results from MELODY for the outcome of RSV MA-LRTIs (150 days post-randomisation) 53
Figure 7. Results of meta-analysis of nirsevimab versus placebo for the outcome of RSV MA-LRTIs (150 days post-randomisation, >=35 wGA) 54
Figure 8. Results from NMA; MA RSV-LRTI (150 days post dose/birth) 57
Figure 9. Random effects meta-analysis of RSV MA-LRTI risk in placebo arms 57
Figure 10. Results from NMA; RSV-associated hospitalisation (150 days post dose/birth) 58
Figure 11. Random effects meta-analysis of RSV hospitalisation risk in placebo arms 58
Figure 12. Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation (MA RSV-LRTI) 59

Figure 13. Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation (RSV-associated hospitalisation) 60
Figure 14 Period of intervention 91
Figure 15 Tornado diagram - nirsevimab vs maternal immunisation – Model 1 96
Figure 16 Tornado diagram - nirsevimab vs SoC - Model 2 97
Figure 17 Scatter plot - nirsevimab vs maternal immunisation – Model 1 99
Figure 18 Scatter plot - nirsevimab vs SoC - Model 2 99
Figure 19 CEAC - nirsevimab vs maternal immunisation – Model 1 99
Figure 20 CEAC - nirsevimab vs SoC - Model 2 99
Figure 21. Treatment network for A: MA-RSV-LRTI and B: RSV hospitalisation 147
Figure 22. PRISMA flowchart for SLR of nirsevimab and Abrysvo 247
Figure 23. PRISMA flowchart for HRQoL SLR 264
Figure 24. Patient disposition in MEDLEY (season 1) 275

Abbreviations

Abbreviation	Meaning
AE(s)	Adverse Event(s)
CEM	Cost-effectiveness model
CHD	Congenital heart disease
CI	Clinical Improvement/Confidence Interval
CLD	Chronic lung disease
DKK	Danish Krone
DMC	Danish Medicines Council
ED	Emergency Department
EMA	European Medicines Agency
GA	Gestational age
GP	General Practitioner
HCRU	Healthcare Resource Utilisation
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IM	Intramuscular
ITC	Indirect Treatment Comparison
IV	Intravenous/intravenously
LRT	Lower respiratory tract
LRTI	Lower respiratory tract infections
LY	Life-Years
MA	Medically attended
mAb	Monoclonal antibody
MI	Maternal immunisation
MiBa	Danish Microbiological Database
NA	Not Applicable
NMA	Network meta-analysis
PC	Primary care
Pre	Preterm infants
PRO	Patient Reported Outcome
PVB	Palivizumab eligible
QALY(s)	Quality-Adjusted Life-Year(s)
QoL	Quality of Life
RNA	Ribonucleic acid
RR	Relative risk

RT-PCR	Reverse transcriptase polymerase chain reaction
SLR	Systematic literature review
SMPC	Summary of product characteristics
SoC	Standard of Care
SSI	Statens Serum Institut
URT	Upper respiratory tract
VE	Vaccine efficacy
WHO	World Health Organisation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Beyfortus
Generic name	Nirsevimab
Therapeutic indication as defined by EMA	Beyfortus is indicated for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in neonates and infants during their first RSV season.
Marketing authorization holder in Denmark	Sanofi
ATC code	J06BD08
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	31 October 2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	Yes
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Solution for injection; 50mg; pre-filled syringe (glass); 0.5 ml (100 mg/ml); 5 pre-filled syringes Solution for injection; 100mg; pre-filled syringe (glass); 1 ml (100 mg/ml); 5 pre-filled syringes

Abbreviations: EMA= European Medicines Agency, RSV= respiratory syncytial virus, EC= European Commission, DMC= Danish Medicines Council

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	This assessment concerns nirsevimab for the prevention of Respiratory RSV lower respiratory tract disease in neonates and infants during their first RSV season.
Dosage regiment and administration	The recommended dose is a single dose of 50mg administered intramuscularly for infants with a body weight <5kg and a single dose of 100mg administered intramuscularly for infants with a body weight ≥5kg.
Choice of comparator	The comparators for this submission are: **1. Standard of Care:** **Infants for whom palivizumab is not indicated:** No prophylaxis, best supportive care. **Infants for whom palivizumab is indicated:** Palivizumab: Prior to the availability of nirsevimab, the only approved and recommended option for RSV prophylaxis was palivizumab, which was granted EMA marketing authorisation in 1999. In Europe, palivizumab is indicated for the prevention of serious LRT disease requiring hospitalisation caused by RSV in children at high risk of RSV disease[1]. In Denmark, palivizumab is recommended for infants born prior to week 32+0 with lung disease and requiring supplemental oxygen, CPAP or mechanical ventilation at week 40 as well as in infants with moderate to severe pulmonary hypertension or hemodynamically significant heart disease. Additionally, palivizumab may be considered in infants with chronic lung disease or conditions with significant or secondary affection of the airways[2]. Palivizumab (15 mg/kg) is given intramuscularly with a monthly interval, rounding up doses to avoid wastage. The first dose should be given before the start of the RSV season, planned around mid-November but may be modified depending on the current season's epidemiology[2]. **2. Maternal immunisation with Abrysvo:** Pregnant women can be vaccinated between 24+0 and 36+0 weeks of gestation[3]. Infants born to vaccinated mothers are immunised from RSV up to 6 months after birth[4].
Prognosis with current treatment (comparator)	**Overall:** The likelihood of hospital admission for children under 1 year of age varies between seasons and by age. Recently, a population-based study in Denmark, found that, between 2010 and 2015, the rate of hospital admissions associated with RSV was 29.4 per 1000 children (< 12 months of age).[5] **Palivizumab:** Palivizumab reduces the risk of severe RSV infection needing hospitalization in high-risk infants when compared to placebo (RR=0.44)[6].
Type of evidence for the clinical evaluation	The MELODY[7], Griffin et al. 2020[8], and HARMONIE[9] trials directly compare nirsevimab to placebo or no intervention.

Summary	
	The MEDLEY trial examined pharmacokinetics, safety and tolerability for nirsevimab compared to palivizumab. The efficacy and safety of maternal immunisation with Abrysvo compared to placebo was examined in the Simoes et al. 2022[10] and MATISSE[3] trials The relative efficacy of nirsevimab versus Abrysvo was examined in a random-effects network meta-analysis
Most important efficacy endpoints (Difference/gain compared to comparator)	**Hospitalisation due to RSV-confirmed lower respiratory tract infection:** *Clinical question 1: Nirsevimab versus palivizumab in palivizumab-eligible infants:* No efficacy data is available for comparison. Based on pharmacokinetics and – dynamics, non-inferiority is assumed. *Clinical question 2: Nirsevimab versus no prophylaxis in pre-term infants:* Nirsevimab versus placebo: risk ratio (RR): 0.208; 95% confidence interval (CI): 0.109 to 0.399 *Clinical question 3: Nirsevimab versus no prophylaxis in term infants:* Nirsevimab versus placebo: risk ratio (RR): 0.196; 95% CI: 0.112 to 0.344 *Clinical question 4: Nirsevimab versus no prophylaxis in term infants* Nirsevimab versus Abrysvo: risk ratio (RR): 0.453; 95% CI: 0.204 to 0.104
Most important serious adverse events for the intervention and comparator	No serious adverse events are associated with neither nirsevimab nor Abrysvo.
Impact on health-related quality of life	The strategies being compared aim at reducing RSV-related hospitalizations and subsequent complications (both short and long term). Improving QoL of infants and their caretakers. The impact on HRQoL is measured by evaluating the efficacy of the interventions to prevent RSV-related hospitalizations, which in turn reduce a baseline HRQoL value in healthy infants.

Summary	
Type of economic analysis that is submitted	The health economic analysis is a cost-utility analysis (ICER, DKK per incremental QALYs) The intervention consists of one intramuscular injection of nirsevimab administered either at the beginning of the first RSV season to infants born before the season, or to newborns born during the season For the palivizumab eligible infants subpopulation the comparator is one monthly dose of palivizumab during the RSV season, as recommended in the recommendation from Dansk Pædiatrisk Selskab.[11] For healthy term and preterm infants, the comparator is no treatment. The health economic model is a decision-analytic model tracking infants over one RSV season where accumulated health outcomes and costs will depend on the selected strategy (i.e., nirsevimab, maternal immunisation, SoC). While the time-horizon of the model will be limited to one RSV season, costs and QALY loss associated with complications will be tracked for three years. QALY loss associated with RSV-related mortality will be calculated based on the life expectancy in Denmark. The model will include costs of treatment (i.e., nirsevimab, maternal immunisation, SoC), health events (e.g., hospitalisations and intensive care), treatment of complications (e.g., recurrent wheezing), and indirect costs (such as transport and time spent for caregivers). Structural and parameter uncertainty is addressed through one-way deterministic sensitivity analyses (OWSAs), probabilistic analyses (PAs), and scenario analyses as applicable.
Data sources used to model the clinical effects	The clinical efficacy of nirsevimab and Abrysvo is based on a network meta-analysis (NMA) comparing nirsevimab, placebo/no intervention, and Abrysvo respectively.
Data sources used to model the health-related quality of life	Given that this assessment concerns infants for one RSV season. HRQoL has been addressed in terms of QALY decrements for RSV-associated hospitalisations and complications. Decrements have been taken from the literature and are presented further discussed in section 0.
Life years gained	Not applicable
Total QALY loss	Nirsevimab vs maternal immunisation (Model 1): • Nirsevimab: [redacted] • Maternal immunisation: [redacted] Nirsevimab vs SoC (Model 2). • Nirsevimab: [redacted] • SoC: [redacted]
Incremental costs (DKK)	Nirsevimab vs maternal immunisation (Model 1): [redacted] Nirsevimab vs SoC (Model 2): [redacted]

Summary	
ICER (DKK/QALY)	Nirsevimab vs maternal immunisation (Model 1): [redacted] Nirsevimab vs SoC (Model 2). [redacted]
Uncertainty associated with the ICER estimate	Nirsevimab vs maternal immunisation (Model 1): The efficacy estimates of nirsevimab in the inpatient setting, the unit cost of nirsevimab and the variance of distribution of RSV infections by month are the most influential parameters. Nirsevimab vs SoC (Model 2): The variance of the distribution of RSV infection by month, the RSV risk by age in term infants, and the unit cost of nirsevimab is the most influential parameters.
Number of eligible patients in Denmark	All infants entering their first RSV season. Assuming all infants will be eligible for nirsevimab, Table 2 in Section 3.2 presents the estimated number of eligible infants between 2025 and 2028, based on population projections from Statistics Denmark[12]. (n=62,239 in 2024). See also Table 61 and Table 62.
Budget impact (in year 5)	Nirsevimab vs maternal immunisation (Model 1): • Palivizumab eligible: [redacted] • Preterm infants: [redacted] • Term infants: [redacted] Nirsevimab vs SoC (Model 2): • Palivizumab eligible: [redacted] • Preterm infants: [redacted] • Term infants: [redacted] For full budget impact, see Table 63 and Table 64

Abbreviations: RSV= respiratory syncytial virus, EMA= European Medicines Agency, LRT= lower respiratory tract, CPAP=, RR= risk ratio, CI= confidence interval, QoL= quality of life, HRQoL= health-related quality of life, ICER= incremental cost-effectiveness ratio, QALY= quality-adjusted life-years, SoC= standard of care

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

RSV is a common, contagious, viral pathogen causing a wide spectrum of respiratory illnesses[13]. RSV is a seasonal virus with two serotypes which can either be present together in a yearly epidemic or alternate[14,15]. RSV is transmitted through airborne droplets, contaminated surfaces, or direct contact with oral or nasal secretions of RSV-positive individuals[16,17]. The incubation period ranges from 3 to 7 days, and people with RSV infection are typically contagious for 3 to 8 days. In more severe cases, a person infected with RSV may be contagious for up to 4 weeks[16,18]. RSV infections occur in people of all

ages; however, they are often more severe and can have fatal outcomes in infants (<12 months of age) with immature immune systems and older adults with weakened immune systems[19]. After the initial infection, RSV replicates in the nasopharynx, and epithelial cells in the upper respiratory tract (URT) are destroyed as the virus replicates[16,20]. The loss of ciliated epithelial cells leads to the accumulation of mucus, resulting in the obstruction of the airway and air trapping[21]. RSV infections that remain in the URT tend to manifest as mild disease, but viral replication can also spread to the lower respiratory tract (LRT), which is typically characterised by a more severe disease course[16,21,22]. RSV infections are a leading cause of lower respiratory tract infections (LRTIs), primarily bronchiolitis and pneumonia, and associated hospitalisations of infants, and are associated with a recurrent and substantial clinical and economic burden[23-26]. Nearly all children will have been infected with RSV by their second birthday[15]. Infants often acquire RSV infections in the community and through other children (e.g., school, child-care centres) and can then transmit to other family members[27]. Infants with siblings are at greater risk of RSV illness compared to those without any siblings[28]. Children with an RSV infection are more likely to transmit RSV to other family members than infected adults and are particularly contagious to immunocompromised elderly family members[29]. Prior to the availability of nirsevimab, there was no EMA approved RSV prophylaxis for healthy infants and no effective antiviral treatment is available.

3.1.1 Virology

RSV is a single-stranded ribonucleic acid (RNA) virus from the *Paramyxoviridae* family[30]. The RSV genome consists of ten genes, which encode eleven structural and non-structural viral proteins[31]. The most important of these proteins are the immunogenic glycoprotein G and fusion protein F, which are crucial for viral infectivity and pathogenesis[30,31]. The G protein mediates attachment to the host cell while the F protein ensures viral entry to host cells through fusion of viral and host cell membranes[30,31]. The F protein also enables fusion of infected cells with neighbouring cells, resulting in the formation of syncytia and mediating viral spread[31].

Variability in the G protein determines RSV serotype, A or B; the F protein exhibits less variability and is largely conserved across serotypes[30,31]. RSV-A and RSV-B may coexist during an epidemic season[30].

3.1.2 Pathogenesis

Transmission of RSV occurs mainly through airborne droplet transmission as well as direct contact with oral or nasal secretions of infected individuals or contaminated surfaces[17,20]. Mucous membranes, typically of the eye, nose, and throat, are the route of entry. After the initial infection, RSV replicates in the nasopharynx over an incubation period of 3 to 7 days[20]. Epithelial cells in the URT are destroyed as the virus replicates and obstruct the airways, leading to the characteristic symptoms associated with RSV[16]. Loss of ciliated epithelial cells leads to the accumulation of mucus and subsequent obstruction of the airway and air trapping[21]. Viral replication can also spread to the LRT, targeting bronchial epithelial cells and alveolus pneumocytes and leading to bronchiolitis and pneumonia[16].

3.1.3 Clinical presentation

RSV infections range from clinically insignificant to severe respiratory distress[16]. RSV infection usually starts in the URT, causing inflammation and similar symptoms to that of

the common cold. Symptoms and clinical presentations of an RSV URT infection include: [15,21,32,33]

- Sneezing, nasal congestion/ rhinorrhoea, dry cough, and croup

RSV infection may also spread to the LRT and manifest as a LRTI (primarily bronchiolitis and/or pneumonia), depending on age and comorbidities[34]. The ability of RSV to damage bronchial airways in infants leads to a high propensity for causing bronchiolitis, with up to 40% of RSV-positive infants developing bronchiolitis after primary infection[35,36]. Symptoms of RSV LRTIs in infants include: [15,33,34,37,38]

- Cough, wheezing/difficulty breathing, tachypnoea (abnormally fast breathing rate), abnormal breath sounds (crackles/rales, rhonchi), diminished breath sounds, chest wall hyper-expansion, nasal flaring, intercostal retractions, hypoxemia, apnoea, fever and/or chills, decreased appetite/poor feeding, irritability, lethargy, and sepsis (in severe cases)

RSV is a leading cause of LRTIs among infants and young children worldwide[26,39], with 60% to 80% of infant bronchiolitis and up to 40% of paediatric pneumonia attributed to the disease[40]. In two prospective studies conducted in Spain and the US RSV was found to be the primary viral cause of LRTIs[1] among hospitalised children aged <2 years (~70% of cases), followed by human rhinovirus (26% of US cases)[41,42]. In a US study conducted between December 2019 and April 2020 of 295 infants with RSV or other acute viral respiratory infections frequently seen in infants (i.e., rhinovirus/enterovirus, influenza), the clinical presentation of RSV infections was typically more severe and associated with a higher rate of hospitalisation than that of other respiratory infections[38]. Infants with RSV were more likely to exhibit cough, shortness of breath, wheezing, crackles, rales and rhonchi, and use of accessory respiratory muscles[38]. These patients also had higher maximum respiratory rates and lower minimum levels of oxygen saturation compared with infants with rhinovirus/enterovirus or influenza[38].

In Denmark, a study from 2021, examined RSV hospitalisation rates between 2010 and 2015 and found that out of 418,404 children born alive in Denmark, 8,959 (2.14%) were hospitalised with RSV within their first year of life[43]. The incidence was highest in early infancy, peaking during the second month of life with almost 60 cases per 1,000 child years, and decreasing to almost no cases around three years of age[43]. Importantly, another study which also examined RSV hospitalisations from between 2010 and 2015, but also included data from the Danish Microbiology Database (MiBa), found a slightly higher hospitalisation rate for children <12 months of 29.4 per 1,000 children[5].

According to the RSV dashboard published by Statens Serum Institut (SSI), among approximately 57,500 infants alive under one year of age between week 21 of 2023 and week 17 of 2024, there were 1402 hospitalisation with a positive RSV sample through the MiBa database, corresponding to a risk of RSV-associated hospitalisation of approximately 2.4%[44].

A severe LRTI is commonly defined as one leading to severe clinical pneumonia (characterised by an acute cough or difficulty in breathing with indrawing of the lower chest wall, with or without fast breathing for age, necessitating hospitalisation)[39]. Hypoxaemia may also be used an indicator of severity in LRTIs[45].

In addition, research shows that RSV infections pose as the single most important risk factor in developing (recurrent) wheezing during the subsequent year. Specifically an odds ratio of 10.92 (wheezing, p<0.001) and 12.10 (recurrent wheezing, p<0.001) between the RSV and control groups[46].

Implementing preventive strategies at the national level yields a twofold clinical benefit: the immediate reduction of RSV-related adverse health events and of long-term complications.

3.1.4 Diagnosis

Among symptomatic individuals who develop clinical illness, diagnosis of RSV infection can be confirmed through laboratory testing of respiratory secretion samples[14]. Rapid antigen detection tests are the most widely used in clinical practice due to a turnaround of <30 minutes and ease of use[47]. Reverse transcriptase polymerase chain reaction (RT-PCR), with a turnaround of a few hours and greater sensitivity than viral culture. In the hospital setting, the diagnosis is made by detection of respiratory syncytial virus (RSV) by PCR in respiratory secretions[48]. The occurrence of laboratory-confirmed RSV cases is monitored using MiBa, where all RS virus tests examined at the country's microbiology departments are included Surveillance of RS virus[48].

3.1.5 Risk factors

RSV infections can manifest as LRTIs, such as bronchiolitis and pneumonia, and cause severe respiratory distress[16,49]. In addition to young age -particularly during the circulation of RSV - physiological risk factors associated with severe RSV infection include:[15,21,23,50,51]

Primary risk factors:

- Preterm birth, chronic lung disease ([CLD] e.g., bronchopulmonary dysplasia), haemodynamically significant congenital heart disease (CHD)

Other risk groups:

- Cystic fibrosis, immunodeficiencies, neuromuscular disorders, Downs syndrome

Infants born just before the RSV season are also at increased individual risk of severe RSV infection and RSV-associated hospitalisations compared with those born at the end of the season[52-56] (see section 3.1.7) .

Due to the complex interaction of multiple risk factors, the risk of severe RSV disease is unpredictable, and all infants are at risk of severe RSV infection that could lead to hospitalisation[57,58]. This is demonstrated by the fact that the majority (between approximately 70% and almost 100%) of infants hospitalised due to RSV are otherwise healthy infants born at term, and up to two thirds of infants admitted to the ICU due to RSV are previously healthy[53,57-65] . Indeed, the number of RSV-positive tests and hospitalisations are similar for infants born before the season and those born in the season[53,66,67].

3.1.6 Mortality

RSV infections are the most common cause of LRTIs in infants and contribute to substantial morbidity and mortality worldwide[26,39,49]. Globally in 2019, RSV-associated LRTIs were estimated to result in 3.6 million hospital admissions each year in children <5 years of age, with almost 61% of hospitalisations occurring in infants aged <12 months[26]. RSV-related morbidity also results in substantial numbers of emergency department and outpatient visits[68]. Global estimates indicate that the overall number of deaths due to RSV-LRTI among children aged <5 years was as high as 101,400 in 2019, accounting for both in-hospital deaths (26,300 estimated in 2019) and community deaths[26].

In Denmark, between 2010 and 2016, out of 12,330 RSV hospitalisations (<5 years of age), five mortalities were linked to the disease, leading to a fatality rate of 0.04%. The median age of the five children was 6.5 months, with four of the patients having serious underlying conditions such as muscular dystrophy, bronchopulmonary dysplasia, and multiple congenital malformations[5]. More recent data from the Danish RSV dashboard published by Statens Serum Institut (SSI) show that one child (<5 years) died following a RSV infection during the 2023/2024 season, one during 2022/2023,and four during the 2021/2022 season[44].

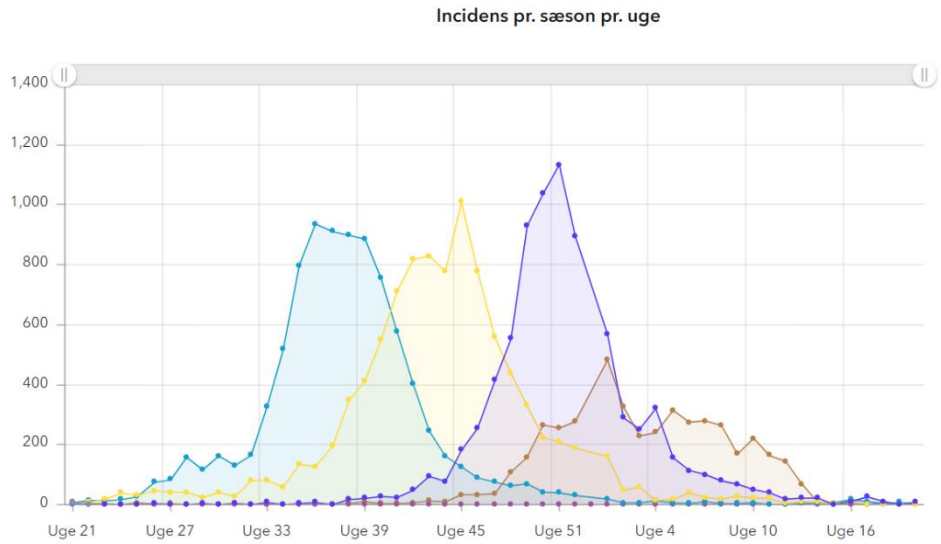
3.1.7 Disease seasonality

RSV exhibits distinct winter seasonality in temperate climates, peaking in late autumn through early spring.[17,69,70]. The RSV season generally begins between September and December in the northern hemisphere, and typically lasts for 4 months[71,72].

As seasonality of the virus may vary from year to year, understanding the yearly RSV patterns contributes to maximising the efficacy of preventive measures such as prophylaxis and immunisation[69,73] .

Figure 1 provides an overview of previous RSV seasons in Denmark between 2017 and 2023. However, seasonality is affected by the COVID-19 pandemic, making the 2020/2021 and 2021/2022 seasons outliers.

Figure 1 Disease seasonality in Denmark (0-5 months of age)



Source: [74]
Note: The SSI RSV Dashboard does not allow for displaying on number of infections for the 0-11 month age group, only the 0-5 month and 6-11 month age group separately. The seasonality pattern for 6-11 months is very similar to that of 0-5 months.

3.2 Patient population

RSV infections are most common in infants (<12 months of age) and older adults[19]. The likelihood of hospital admission for children under 1 year of age varies between seasons and by age. A population-based study in Denmark, found that, between 2010 and 2015, the average annual rate of hospital admissions associated with RSV was 29.4 per 1000 children (< 12 months of age)[5]. An advantage of this study was that it was based on both RSV specific diagnosis codes and MiBa data.

Based on gestational age at birth, infants have different risks of RSV-related adverse events[75]. For this analysis the main subgroups defined in terms of risks are:

- Preterm infants who are palivizumab eligible
- Preterm infants that are not eligible for palivizumab (born at or before 34wGA)
- Term infants (born after 35wGA)

Table 1 Incidence and prevalence of lab-confirmed RSV in the past 5 years

Year	2019/2020 season	2020/2021* season	2021/2022 season	2022/2023 season	2023/2024 season
Incidence in Denmark (0-5 months)	4,703.7	13.3*	9,862.6	10,437.4	8,334.3
Incidence in Denmark (6-11 months)	1,799.3	0*	4,227.9	3,610.3	3,753.0
Prevalence in Denmark	NA	NA	NA	NA	NA

* COVID-19 lockdown season
Incidence: confirmed cases per 100,000 infants in that age group
No prevalence reported due to disease lasting one season.
Source:[44]
Abbreviations: NA= not available / not applicable

Assuming all infants will be eligible for nirsevimab, Table 2 presents the estimated number of eligible infants between 2025 and 2028, based on population projections from Statistics Denmark[12].

Table 2 Estimated number of infants eligible for treatment (population projections)

Year	2025	2026	2027	2028	2029
Number of infants in Denmark eligible for treatment in the coming years	62,239	65,590	67,375	70,037	71,781

3.3 Current treatment options

There are currently no effective treatments against active RSV infection; in the following, prophylactic options, rather than treatments, are discussed.

Currently no national guidelines are available for the prevention of RSV infections in all infants. Palivizumab can be used for prophylaxis in high-risk infants, following country-specific guidelines.

3.3.1 Prophylaxis with palivizumab

Prior to the availability of nirsevimab, the only approved and recommended option for RSV prophylaxis was palivizumab, which was granted EMA marketing authorisation in 1999. In Europe, palivizumab is indicated for the prevention of serious LRT disease requiring hospitalisation caused by RSV in children at high risk of RSV disease[1].

In Denmark, palivizumab is recommended for infants born prior to week 32+0 with lung disease and requiring supplemental oxygen, CPAP or mechanical ventilation at week 40 as well as in infants with moderate to severe pulmonary hypertension or hemodynamically significant heart disease. Additionally, palivizumab may be considered in infants with chronic lung disease or conditions with significant or secondary affection of the airways.

Palivizumab (15 mg/kg) is given intramuscularly with a monthly interval, rounding up doses to avoid wastage. The first dose should be given before the start of the RSV season, planned around mid-November but may be modified depending on the epidemiology of the current season.

Results from clinical trials show efficacy of palivizumab in high-risk groups only. The first pivotal trial in 1998 reported a 55% overall reduction in RSV-associated hospitalisations in infants aged ≤6 months with ≤35 weeks gestational age and children aged ≤24 months with BPD immunised with palivizumab vs. placebo (4.8% vs. 10.6%)[76]. Results of real-word studies of palivizumab indicate that the monthly injection requirements can elicit poor adherence and consequently decrease efficacy[77,78].

It should be noted that the Danish Pediatric Society updated their recommendations for RSV prophylaxis in November 2023, and now recommend nirsevimab over palivizumab for prevention of RSV in high-risk children; as nirsevimab is currently not available on the Danish market, the recommendation states that when nirsevimab is not available, palivizumab should be used as before[2].

3.3.2 Maternal immunisation

Abrysvo is a bivalent, recombinant RSV prefusion F-protein subunit vaccine, which is approved for active immunization of people over 60 and pregnant women. Passive protection of infants against lower respiratory tract infection with RSV from birth to 6 months of age[4]. Vaccination of pregnant women is administered between 24 and 36 weeks of gestation. In a large, randomized, double-blind, placebo-controlled phase 3 multicentre study including approx. 3600 mothers in both the vaccine group and the placebo group. Vaccine efficacy (VE) was measured as (1−RR)×100, where RR was the relative risk of the end point of interest based on the incidence in the vaccine group as compared with the placebo group. VE against severe medically observed RSV-associated lower respiratory tract infection in infants and found to be 69.4% (95% CI: 44.3%-84.1%). VE against all medically observed RSV-associated lower respiratory tract infection was 51.3% (95% CI: 29.4%-66.8%) and VE against RSV-associated hospitalization was 56.8% (95% CI: 10.1 %-80.7%) within 180 days after birth[79]. Vaccine efficacy has been found to be higher with vaccination later in pregnancy. The VE for severe medically observed lower respiratory tract disease was 57.2% (95% CI: 10.4, 80.9) for children whose mothers were vaccinated at GA 24 to < 30 weeks, and 78.1% (95% CI: 52.1, 91.2) for children whose mother was

vaccinated at GA 30 to 36 weeks. VE for medically observed lower respiratory tract disease was 30.9% (95% CI: -14.4, 58.9) for children whose mother was vaccinated at GA 24 to < 30 weeks, and 62.4% (95% CI: 41.6; 76.4) for children whose mother was vaccinated in GA 30 to 36 weeks[4]. These findings await confirmation in real-life efficacy studies.

Maternal immunisation with Abrysvo is not a part of current practice; however, as Sundhedsstyrelsen is considering an RSV prevention program, Sanofi was asked to include maternal immunisation with Abrysvo as a second comparator.

3.4 The intervention

3.4.1 Nirsevimab

Nirsevimab is a recombinant neutralising human IgG1κ long-acting monoclonal antibody (mAb) against the prefusion conformation of the RSV F protein. It has been modified with a triple amino acid substitution (YTE) in the Fc region to extend serum half-life up to approximately 69 days (terminal half-life). Nirsevimab binds with high affinity to a highly conserved epitope on the prefusion protein (antigenic site Ø). The dissociation constant (K_D) is 0.12nM for RSV subtype A and 1.22nM for RSV subtype B. Nirsevimab inhibits the membrane fusion step in the viral entry process, neutralising the virus and blocking cell-to-cell fusion.

Based on clinical and pharmacokinetic data, nirsevimab has a duration of protection of at least 5 months[80]. Nirsevimab can be administered concomitantly with paediatric vaccines. Nirsevimab is a passive immunisation specific for RSV and therefore is not expected to interfere with active immune responses to co-administered vaccines[5]. Nirsevimab was administered with routine paediatric vaccines in clinical trials and the safety and reactogenicity profile of the co-administered regimen was similar to the paediatric vaccines given alone[81].

Overview of intervention	Nirsevimab
Therapeutic indication relevant for the assessment	This assessment concerns nirsevimab for the prevention of RSV lower respiratory tract disease in neonates and infants during their first RSV season.
Method of administration	Intramuscular injection
Dosing	The recommended dose is a single dose of 50mg administered intramuscularly for infants with body weight <5kg and a single dose of 100mg administered intramuscularly for infants with body weight ≥5kg.
Dosing in the health economic model (including relative dose intensity)	Dependent on infant weight: ≤5 kg: 50mg > 5kg: 100mg
Should the medicine be administered with other medicines?	No

Overview of intervention	Nirsevimab
Treatment duration / criteria for end of treatment	Injection at the beginning of RSV season for infants born before the season and at birth for infants born during the season to cover at season of at least 150 days[82]
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Solution for injection; 50mg; pre-filled syringe (glass); 0.5 ml (100 mg/ml); 5 pre-filled syringes Solution for injection; 100mg; pre-filled syringe (glass); 1 ml (100 mg/ml); 5 pre-filled syringes

Abbreviations: RSV, respiratory syncytial virus

3.4.2 The intervention in relation to Danish clinical practice

The introduction of nirsevimab as a preventive measure for RSV infections is expected to replace the use of prophylaxis with palivizumab in high-risk infants.

Currently no widespread prophylaxis or prevention program exists in Denmark. The introduction of nirsevimab for all the infants born in the RSV season would lead to a dramatic reduction of RSV cases, easing the overall pressure on the healthcare system, as well as lessen the humanistic burden associated with RSV-related morbidity and hospitalisations.

3.5 Choice of comparator(s)

The relevant comparators for this submission are standard of care (best supportive care or palivizumab) and maternal immunisation. Comparators are further discussed in the following section.

3.5.1 Standard of care for the prevention of RSV

In Denmark, prophylaxis is currently only administer to infants considered at particularly high risk (as defined in the guidelines from the Danish Pediatric Society[2]).

High risk infants:
Prophylaxis with Palivizumab (trade name Synagis)

Overview of comparator	Synagis
Generic name	Palivizumab
ATC code	J06BD01

Overview of comparator	Synagis
Mechanism of action	Palivizumab is a humanised IgG1 monoclonal antibody directed to an epitope in the A antigenic site of the fusion protein of respiratory syncytial virus (RSV). This humanised monoclonal antibody is composed of human (95%) and murine (5%) antibody sequences. It has potent neutralising and fusion-inhibitory activity against both RSV subtype A and B strains
Method of administration	Palivizumab is administered intramuscularly, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The injection should be given using standard aseptic technique.
Dosing	The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should be administered prior to commencement of the RSV season. Subsequent doses should be administered monthly throughout the RSV season. The efficacy of palivizumab at doses other than 15 mg per kg or of dosing differently from monthly throughout the RSV season, has not been established.
Dosing in the health economic model (including relative dose intensity)	Dependent on weight; 15mg/kg.
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Once a month when there is a risk of RSV infection in the community. Patients generally should receive a total of up to five monthly injections into the thigh muscle
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Synagis 50 mg/0.5 ml solution for injection Synagis 100 mg/1 ml solution for injection

Abbreviations: IgG1, Immunoglobulin G 1; RSV, respiratory syncytial virus

Source: Synagis SMPC[1]

3.5.2 Maternal immunisation

In August 2023, EMA issued a marketing authorisation for Abrysvo. The medicinal product can be used in mothers during pregnancy to immunise their infant from LRTD caused by RSV.

Overview of comparator	Abrysvo
Generic name	Respiratory syncytial virus vaccine (bivalent, recombinant)
ATC code	J07BX05
Mechanism of action	In infants born to mothers who were vaccinated with Abrysvo between weeks 24 and 36 of gestation, protection against RSV-associated lower respiratory tract disease is due to transplacental transfer of RSV neutralising antibodies.
Method of administration	Abrysvo is for intramuscular injection into the deltoid region of the upper arm.
Dosing	Pregnant individuals: A single dose of 0.5 mL should be administered between weeks 24 and 36 of gestation.
Dosing in the health economic model (including relative dose intensity)	0.5ml
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Pack containing 1 vial of powder (antigens), 1 pre-filled syringe of solvent, 1 vial adaptor with 1 needle or without needles (1 dose pack). Pack containing 5 vials of powder (antigens), 5 pre-filled syringes of solvent, 5 vial adaptors with 5 needles or without needles (5 dose pack). Pack containing 10 vials of powder (antigens), 10 pre-filled syringes of solvent, 10 vial adaptors with 10 needles or without needles (10 dose pack). Pack containing 5 vials of powder (antigens) and 5 vials of solvent (5 dose pack).

Abbreviations: RSV, respiratory syncytial virus; NA, not available

Source: Abrysvo SMPC[4]

3.6 Cost-effectiveness of the comparator(s)

The two main comparators relevant for this submission are SoC (consisting of palivizumab for high-risk infants and no prophylaxis for other infants) and maternal immunisation with Abrysvo. Neither of the treatment alternatives have been evaluated by the DMC; however, SoC consists of palivizumab for a very small number of infants and no prophylaxis for all other infants, and as thus can be considered cost-effective for the purpose of this submission.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Efficacy outcomes relevant for this submission are:

- RSV associated hospitalizations
- Very severe RSV associated LRTI (As defined in HARMONIE)
- Medically attended RSV-related LRTI

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Medically attended RSV lower respiratory tract infection (MELODY, MEDLEY, Griffin et al 2020)	150 days post dose	Positive RSV PCR test performed at a central laboratory + Documented physical examination indicating involvement of the lower respiratory tract (Rhonchi, Rales, Crackles, Wheeze) (Medley, Melody, Harmonie)	See definition
Very severe RSV-associated LRTI (HARMONIE)	One RSV season up to 180 days post dose (2022/2023)	Hospitalization for RSV-associated LRTI with an oxygen saturation of less than 90% and the need for supplemental oxygen, with RSV testing done according to hospital policy (HARMONIE)	See definition
Medically attended RSV-associated hospitalizations (MELODY, HARMONIE, Griffin et al 2020)	150 days post dose	RSV hospitalization is defined as either: 1) a respiratory hospitalization with a positive RSV test after hospital admission 2) a new onset of respiratory symptoms in an already hospitalized subject, with an objective measure of worsening respiratory status and positive RSV test (nosocomial). (Medley) 3) hospital admission and an RSV-positive test result (HARMONIE)	Monitoring of study subjects by the investigators at the time of hospitalization

* Time points for data collection used in analysis (follow up time for time-to-event measures)
Abbreviations: RSV, Respiratory syncytial virus

Validity of outcomes

The outcomes of medically attended RSV-LRTI, RSV-associated hospitalisations, and severe RSV-LRTIs have clear clinical relevance, and are commonly used outcomes[82] in clinical trials of RSV prevention.

RSV associated hospitalizations have been used in the literature to assess RSV epidemiology and disease impact in Denmark[5,44]. Additionally, hospitalisations are also used as a metric in Danish treatment guidelines for palivizumab eligibility[11]. RSV associated hospitalisations and LTRI are also used in expert consensus papers[83].

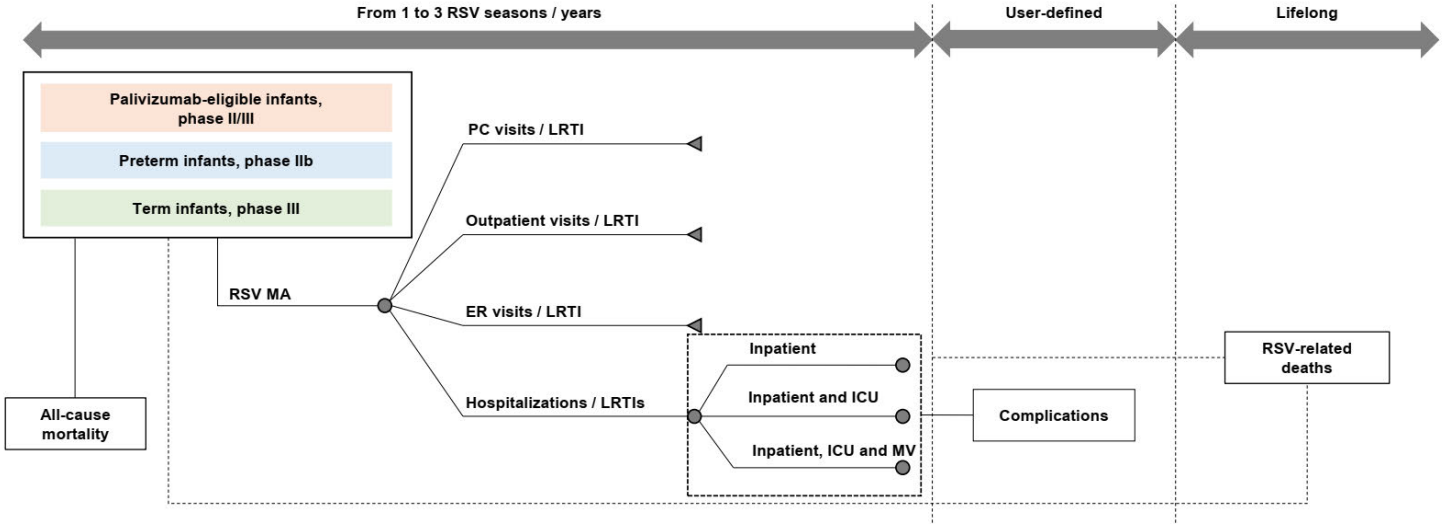
4. Health economic analysis

The cost-effectiveness analysis was based on a Danish adaptation of an Excel-based static decision analytic model. The objective of the model is to assess the cost-effectiveness of nirsevimab versus SoC and nirsevimab versus maternal immunization in infants. Therefore, after agreement with the DMC, we have submitted two models to reflect both comparative scenarios. The estimated effect of nirsevimab and Abrysvo is based on randomised clinical trials. Danish registry or virus surveillance data is used for most of the input data (e.g., births distributions by month). The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained. The following section (4.1) introduces the model structure and its features.

4.1 Model structure

The static decision analytic model (decision tree) tracks one cohort of infants over one RSV season, comparing two immunization strategies (nirsevimab and MI) and accumulating the associated RSV-related health outcomes and costs. Figure 2 illustrates the model structure implemented in the current analysis. The model can consider either the overall infant population or stratified subpopulations. Subpopulations are defined in earlier section 3.2 and outlined in Table 4.

Figure 2 Model structure



Abbreviations: ER= emergency room, ICU= In the Danish setting, ICU is taken to mean intensive care or observation, whether in the pediatric department or in specialised intensive care units, LRTI= lower respiratory tract illness, MA= medially attended, MV= mechanical ventilation, PC= primary care, RSV= respiratory syncytial virus

The model follows three key dimensions:

The first dimension involves the definition of the RSV season and infant age at the start of the defined season. Infants enter the model in monthly birth cohorts such that the first cohort to enter the model corresponds to infants born in the month immediately after the preceding RSV season. In the base-case analysis, as the RSV season extends from November to February, the oldest infants experiencing their first RSV season are born in May and will enter their first RSV season at seven months of age.

The second dimension reflects the distribution of RSV cases throughout the year. As both nirsevimab and maternal immunisation offer a time-limited window of protection, the delineation of the distribution of RSV cases throughout the year can inform when protection against infection is the most needed.

The third dimension involves the rate of RSV-related healthcare resource use by age in months. While healthcare resource use associated with RSV-related events is expected to be higher in younger infants, by applying an age-dependent risk of RSV-related health events, the analysis can accurately track the associated burden of RSV.

The combination of the three key dimensions allows to precisely define the burden of disease per calendar month and age. Infants enter the model in monthly birth cohorts and can be stratified by three subpopulations, palivizumab eligible preterm infants, preterm infants, and term infants (see section 4.1.1). Each monthly cohort is then tracked separately across the specified time horizon. Infants receive either standard of practice care, nirsevimab or maternal immunisation. The two active strategies have different efficacy, coverage rate, and duration of protection which are applied to infants. As a consequence of receiving either strategy, infants experience a reduction in the risk of RSV-related health events during the window of protection. An individual patient risk of RSV by age and health event are applied to determine the number of RSV-related health events requiring medical resource use (inpatient hospitalization, intensive care and observation visits, mechanical ventilation [MV], emergency room [ER] visits, and primary care [PC] visits).

The quality-adjusted life year (QALY) losses and costs associated with each health event are estimated based on the total case counts to determine the total QALY losses and costs associated with each immunization strategy. Then, the incremental health event cases, QALY losses, and costs are compared between the two strategies. The main outcome produced by the model is the incremental cost-effectiveness ratio (ICER) at a given acquisition cost, which is calculated to determine the impact of introducing nirsevimab for prevention of RSV in infants vs. the standard of practice care, and vs maternal immunisation.

4.1.1 Subpopulations in the model

The goal of the subpopulation structure was to consider the different individual risks of RSV-related health events; from the highest risk (palivizumab-eligible infants) to the lowest risk (healthy term infants). Each of the subpopulations was disaggregated by month of birth and for increased granularity in estimating the burden of disease and assessing

the impact of different strategies. The analyses can also be applied to the overall infant population by applying a single set of inputs evenly across the different subpopulations.

- **Palivizumab-eligible infants:** Infants eligible for palivizumab prophylaxis according to the recommendations from the Danish Pediatric Society[2].
- **Preterm infants:** Infants born at or before 34 weeks and six days of gestational age (not eligible for prophylaxis with palivizumab).
- **Term infants:** Infants born at or after 35 wGA (not eligible for prophylaxis with palivizumab).

The subpopulations correspond to the three groups assessed in the nirsevimab clinical trials, although there are slight variations in when an infant is considered palivizumab eligible. Specifically, the safety and tolerability of nirsevimab was assessed in the palivizumab-eligible population in the phase II/III MEDLEY study[75]; preterm infants were studied in the phase IIb trial[8], while term and late preterm infants (hereafter defined as "term" to improve readability) constituted the population of interest in the phase III MELODY trial[7].

4.2 Model features

Table 4 describes the model features.

Table 4 Model features

Model features	Description	Justification
Patient population	Infants entering their first RSV-season, divided into the following subpopulations: 1) Palivizumab-eligible infants 2) preterm infants 3) term infants. See section 4.1.1 for further description.	To account for the different individual risks of medically-attended lower respiratory tract infections (LRTIs) and other RSV-related health events. The subpopulations correspond to the three groups assessed in the nirsevimab clinical trials [7,8,75]
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	The model conducts the analysis over one RSV season such that infant outcomes are tracked, and costs are accrued only during the specified RSV season. There are a few exceptions with longer time horizons: 1) Complications – risk of complications is defined as a one-time risk over the lifetime of the infant, and 2) RSV related mortality – a lifetime time horizon. See further description in Section 8.4, Table 27. Assumptions and inputs used in the base case in the health economic model	Based on data availability, indication, and that the prevention of medically attended RSV infections is only expected to be considered relevant for infants entering their first RSV season.
Cycle length	N/A	N/A

Model features	Description	Justification
Half-cycle correction	N/A	N/A
Discount rate	3.5 % The discount rate in the Excel model in the sheet "Settings" only effect the RSV related mortality and recurrent wheezing.	As per DMC's guidelines.
Intervention	Nirsevimab	
Comparator(s)	SoC Maternal immunisation	Per agreement with the DMC
Outcomes	RSV-associated hospitalisations	The model is driven by a reduction in RSV-hospitalisation (and a subsequent reduction in intensive care, mechanical ventilation, and complications) as well as reduction in medically attended RSV in the outpatient setting. These reductions are based on the listed efficacy outcomes.

Abbreviations: DMC= Danish medicines council, LTRI= lower trait respiratory infections, SoC= standard of care, RSV= Respiratory syncytial virus

5. Overview of literature

5.1 Literature used for the clinical assessment

As part of this DMC application, a systematic literature review (SLR) was conducted to identify relevant interventional and observational studies examining the efficacy and/or safety of nirsevimab and Abrysvo. A summary of the SLR is provided below; full methods and results (including the PRISMA flowchart and search results) are provided in Appendix H.

The systematic literature review (SLR) described involves three main stages:

1. Comprehensive Search: A detailed search of published literature was conducted to identify all studies potentially relevant to the review.
2. Study Selection: Studies were systematically selected based on predefined inclusion and exclusion criteria to collate the main body of clinical evidence.
3. Data Extraction: Relevant data was extracted from the selected studies to evaluate clinical evidence across various therapeutic options.

Search Details:

Databases: Searches included major electronic databases like Embase® and MEDLINE® via Ovid.com, and The Cochrane Library which includes the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials. The search strategies and specifics are detailed in Appendix H.

Clinical Trial Registries: Additional records were identified from clinical trial registries such as Clinicaltrials.gov and the EU Clinical Trial Register. Details of these search strategies are in Appendix H.

The search did not have time restrictions, and efforts were made to capture all relevant clinical studies through initial searches and screening of bibliographies. No language restrictions were applied.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. New England journal of medicine 2022; 386(9): 837-46.[7]	MELODY	NCT03979313	Start: 23/7/2019 Completion: 21/3/2023 Data cut-off: Final Future data cut-offs: None	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo
Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. New England journal of medicine 2020; 383(5): 415-25.[84]	Griffin et al. 2020	NCT02878330	Start: 3/11/2016 Completion: 17/7/2018 Data cut-off: Final Future data cut-offs: None	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo
Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. New England journal of medicine 2023; 389(26): 2425-35.[9]	HARMONIE	NCT05437510	Start: 8/8/2022 Completion: 14/3/2025 Data cut-off: Interim Analysis Future data cut-offs: Final data upon completion	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo
Domachowske J, Madhi SA, Simões EAF, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. New England	MEDLEY	NCT03959488	Start: 30/7/2019 Completion: 20/1/2023 Data cut-off: Final Future data cut-offs: None	Safety of nirsevimab versus palivizumab for the prevention of RSV in palivizumab-eligible infants

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
journal of medicine 2022; 386(9): 892-4.[85]				
Simões EAF, Tita ATN, Swanson KA, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *New England journal of medicine* 2022; 386(17): 1615-26.[10]	Simoes et al. 2022	NCT04032093	Start: 7/8/2023 Completion: 30/9/2021 Data cut-off: Unclear Future data cut-offs: Unclear	Indirect comparison of nirsevimab versus Abrysvo
Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. New England journal of medicine 2023; 388(16): 1451-64.[3]	MATISSE	NCT04424316	Start: 17/20/2020 Completion: 27/10/2023 Data cut-off: Interim analysis Future data cut-offs: Unclear	Indirect comparison of nirsevimab versus Abrysvo

* If there are several publications connected to a trial, include all publications used.

Abbreviations: RSV= Respiratory syncytial virus

5.2 Literature used for the assessment of health-related quality of life

As part of this DMC application, a systematic literature review of HRQoL data was conducted to identify relevant interventional and observational studies. A summary of the HRQoL SLR is provided below; full methods and results (including the PRISMA flowchart and search results) are provided in Appendix IAppendix H. Due to the problems associated with estimating HRQoL in infants, a relatively specific search string has been utilized. In addition, given that infants are not able to complete standard HRQoL instruments, only studies estimating utility decrements and/or QALD/Y loss were included in the review. Evidence from the two selected studies was used to inform the QALD/Y loss associated with each RSV-related adverse event (see section 0)

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 0)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Mao Z, Li X, Dacosta-Urbieta A, et al. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. *Vaccine* 2023; 41(16): 2707-15. [86]	QALY loss per RVS-related adverse event	Section 10
Li X, Bilcke J, Fernández LV, et al. Cost-effectiveness of Respiratory Syncytial Virus Disease Prevention Strategies: Maternal Vaccine Versus Seasonal or Year-Round Monoclonal Antibody Program in Norwegian Children. *J Infect Dis* 2022; **jiac064**. [87]	Annual QALY loss per complication (wheezing & asthma)	Section 10

Abbreviations: QALY= quality adjusted life years, RSV= Respiratory syncytial virus

5.3 Literature used for inputs for the health economic model

No systematic literature review was carried out to inform inputs of the health economic model. However, targeted literature reviews were done to identify Danish data for relevant model inputs. In addition, data from publicly available sources (e.g., the RSV Dashboard from SSI[44], and Danish registries[88]) were used where possible. The inputs that needed to be adapted to a Danish setting mainly consisted of distributions of births by month, distributions of RSV infections by month, and the proportions of RSV hospitalisations stratified by risk group. The two studies selected in the HRQoL SLR were also used to inform inputs of the CEM . Table 7 presents an overview of the identified literature used in the health economic model.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Statistics Denmark. BEV3A: Levendefødte og døde på måneder. 2024. www.statistikbanken.dk/BEV3A[89]	Number of births in Denmark Distribution of births by months	Targeted literature review	Section 8.4 Table 27
Statens Serum Institut. RSV Dashboard. 2024. https://experience.arcgis.com/experience/220fef27d07d438889d651cc2e00076c/page/RS-virus/2024)[44]	Distribution of RSV infections by month (to inform timing and duration of season) Risk of RSV-hospitalisation	Targeted literature review	Section 8.4 Table 27
eSundhed. Nyfødte og fødsler (1997-); Graviditet: Graviditetslængde (niveau 2). 2024. https://www.esundhed.dk/Emner/Graviditet-foedsler-og-boern/Nyfoedte-og-foedsler-1997-[90]	Distribution of births by gestational age	Targeted literature review	Section 8.4 Table 27
Mira-Iglesias A, Demont C, Lopez-Labrador FX, et al. Role of age and birth month in infants hospitalized with RSV-confirmed disease in the Valencia Region, Spain. Influenza Other Respir Viruses 2022; 16(2): 328-39.[91]	Distribution of RSV hospitalisations by month of age	Targeted literature review	Section 8.4 Table 27
Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics* 2013; **132**(2): e341-8.[92]	Distribution of hospitalisation risk across subpopulations	Targeted literature review	Section 8.4 Table 27
Feltes TF, Simoes E. Palivizumab prophylaxis in haemodynamically significant congenital heart disease. *Arch Dis Child* 2005; **90**(8): 875-7; author reply -7.[93]	Distribution of hospitalisation risk across subpopulations	Targeted literature review	Section 8.4 Table 27
The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics* 1998; **102**(3 Pt 1): 531-7.[94]	Distribution of hospitalisation risk across subpopulations	Targeted literature review	Section 8.4 Table 27

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Sanofi. Data on RSV hospitalisations from Danish registries [Data on file]. 2024.[88]	Proportion of hospitalised infants receiving intensive observation/care or mechanical ventilation	N/A	Section 8.4 Table 27
Arriola CS, Kim L, Langley G, et al. Estimated Burden of Community-Onset Respiratory Syncytial Virus-Associated Hospitalizations Among Children Aged <2 Years in the United States, 2014-15. J Pediatric Infect Dis Soc 2020; 9(5): 587-95.[95]	Distribution of risk of intensive care or mechanical ventilation between subpopulations	Targeted literature review	Section 8.4 Table 27
Simoes EAF, Madhi SA, Muller WJ, et al. 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. Lancet Child Adolesc Health 2023; 7(3): 180-9.[96]	Preventive efficacy of nirsevimab	Targeted literature review	Section 8.4 Table 27
Simões EAF, Tita ATN, Swanson KA, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *New England journal of medicine* 2022; **386**(17): 1615-26.[10]	Used in NMA to obtain preventive efficacy of Abrysvo	Clinical SLR	Section 6 Section 7
Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. New England journal of medicine 2023; 388(16): 1451-64.[3]	Used in NMA to obtain preventive efficacy of Abrysvo	Clinical SLR	Section 6 Section 7
Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2024; 29(4).[97]	Used to estimate coverage rates for nirsevimab	Clinical SLR	Section 8.4 Table 27
Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *The Lancet Infectious Diseases* 2024.[98]	Used to estimate coverage rates for nirsevimab	Clinical SLR	Section 6 Section 8.4 Table 27

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Sundhedsstyrelsen, Lægemiddelstyrelsen, Statens Serum Institut. Årsrapport - Børnevaccinationsprogrammet 2023. 2024.[48]	Used to estimate coverage rates for Abrysvo (assumed to be similar to those of the pertussis maternal immunization program)	Targeted literature review	Section 8.4 Table 27
Mao Z, Li X, Dacosta-Urbieta A, et al. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. *Vaccine* 2023; 41(16): 2707-15. [86]	QALY loss per RVS-related health event	Targeted literature review	Section 10
Li X, Bilcke J, Fernández LV, et al. Cost-effectiveness of Respiratory Syncytial Virus Disease Prevention Strategies: Maternal Vaccine Versus Seasonal or Year-Round Monoclonal Antibody Program in Norwegian Children. *J Infect Dis* 2022; **jiac064**.[87]	Annual QALY loss per complication (wheezing & asthma)	Targeted literature review	Section 10

Abbreviations: NMA= network meta analysis, QALY= quality adjusted life year, RSV= Respiratory syncytial virus

6. Efficacy

6.1 Efficacy of nirsevimab versus Abrysvo for prevention of RSV infection in infants

6.1.1 Relevant studies

The studies considered relevant for the efficacy of nirsevimab compared to Abrysvo are shown in Table 8. The MEDLEY trial was not an efficacy trial - examined pharmacokinetics, safety and tolerability in palivizumab eligible children[85] - and is not discussed below, but the safety results from MEDLEY are provided in Appendix K.

In addition to the randomised trials informing efficacy of nirsevimab and Abrysvo identified and described in Table 8, several real-world evidence studies of nirsevimab were identified in the clinical SLR. While these do not inform the health-economic model and are not included in the indirect comparison, they are briefly described in section 6.1.9.

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Primary outcomes and follow-up period
MELODY Hammitt et al. 2022[99] (NCT03979313)	Phase 3, randomised, double-blind, placebo-controlled study	Participants were followed for up to 361 days after dosing.	Healthy late preterm and term infants (GA ≥ 35+0 weeks)	Nirsevimab	Placebo	Number of Participants With MA RSV LRTI Through 150 Days Post Dose.
Griffin et al. 2020[84] (NCT02878330)	Phase 2b, randomised, double-blind, placebo-controlled study	From Day 1 through up to Day 361 depending on outcome.	Healthy preterm infants (GA between 29+0 and 34+6 weeks)	Nirsevimab 50 mg	Placebo	Number of Participants With MA RSV LRTI From Day 1 through Day 151. From Day 1 through up to Day 361 depending on outcome.
HARMONIE Drysdale et al. 2023[9] (NCT05437510)	Phase 3b, randomised, open-label study	Ongoing (efficacy results available) Participants will be followed for up to 24 months after dosing, depending on outcome and country of residence.	Healthy term and preterm infants (GA ≥ 29+0 weeks)	Nirsevimab	No intervention	Overall incidence of RSV LRTI hospitalization through the RSV season
Simoes et al. 2022[10] (NCT04032093)	Phase 2b, randomised, placebo-controlled, observer-blinded trial	Maternal participants were followed up to 12 months after delivery. Infant participants were followed up to 12 months after birth.	Infants born to healthy women 18-49 years of age, vaccinated between 24 and 36 weeks of gestation	Abrysvo	Placebo	Percentage of Infant Participants With Specific Birth Complications, percentage of Infant Participants With Any AE Within 1 Month of Age, percentage of Infant Participants With MAEs and SAEs Within 12 Months of Age, and percentage of Infant Participants With AEs of Special Interest of at Least Moderate Severity Within 12 Months of Age:
MATISSE Kampmann et al. 2023[3] (NCT04424316)	Phase 3, randomised, double-blind, placebo-controlled trial	From birth up to 24 months of age depending on outcome	Infants born to healthy women under 49 years of age, vaccinated between 24+0 and 36+0 weeks of gestation	Abrysvo	Placebo	The percentage reduction in the incidence of RSV MA-LRTI and severe RSV MA-LRTI in infants through 180 days of life

Abbreviations: GA= Gestational age, AE= adverse event, MA= medically attended, LRTI= Lower respiratory tract infections, SAE= serious adverse event, RSV= Respiratory syncytial virus

6.1.2 Comparability of studies

Nirsevimab, a monoclonal antibody administered to the infant, and Abrysvo, a vaccine administered to the mother, who then transfers antibodies to the foetus, are conceptually different. Because of this difference, the clinical trial programs for nirsevimab and Abrysvo have some key differences.

In the trials of nirsevimab, infants are included in the trial, whereas the Abrysvo trials include pregnant women and subsequently the infants after they are born. Thus, in the nirsevimab trials, outcome time points are defined as a designated period after administration of nirsevimab (generally 150 days), while the outcome time points for the Abrysvo trials are defined as a designated period post-birth. Additionally, the design of the nirsevimab trials allows for specific inclusion and exclusion criteria of the infants (e.g., based on gestational age at birth), whereas the Abrysvo trials apply inclusion and exclusion criteria to the mothers, and then include all children born to the included mothers. These differences aside, the efficacy studies use similar methods to estimate the relative efficacy, and all use either placebo or no-intervention as the comparator.

6.1.2.1 Comparability of patients across studies

Baseline characteristics for the studies considered relevant for the analyses of efficacy are presented in Table 9. Due to the differences between nirsevimab and Abrysvo (nirsevimab is administered to infants at the start of or during the RSV season, whereas Abrysvo is administered to the pregnant woman) some baseline characteristics are not directly comparable. Additionally, there were slight differences between studies in how baseline characteristics were reported.

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	MELODY*		Griffin et al. 2020		HARMONIE		Simoes et al. 2022**					MATISSE	
	Nirsevimab (n=994)	Placebo (n=496)	Nirsevimab (n=969)	Placebo (n=484)	Nirsevimab (n=4037)	Placebo (n=4021)	Abrysvo (120 µg, n=79)	Abrysvo (120 µg + Al(OH)3, n=84)	Abrysvo (240 µg, n=78)	Abrysvo (240 µg + Al(OH)3, n=86)	Placebo (n=79)	Nirsevimab (n=3568)	Placebo (n=3558)
Age[a], n (%)													
≤ 3 months	577 (58.0%)	285 (57.5%)	516 (53.3%)	257 (53.1%)	1962 (48.6%)	1954 (48.6%)	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
> 3 to < 6 months	317 (31.9%)	162 (32.7%)	320 (33.0%)	153 (31.6%)	959 (23.8%)	953 (23.7%)	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant
> 6 months	100 (10.1%)	49 (9.9%)	133 (13.7%)	74 (15.3%)	1116 (27.6%)	1114 (27.7%)	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant	Not relevant

	MELODY*		Griffin et al. 2020		HARMONIE		Simoes et al. 2022**					MATISSE	
	Nirsevimab (n=994)	Placebo (n=496)	Nirsevimab (n=969)	Placebo (n=484)	Nirsevimab (n=4037)	Placebo (n=4021)	Abrysvo (120 µg, n=79)	Abrysvo (120 µg + Al(OH)3, n=84)	Abrysvo (240 µg, n=78)	Abrysvo (240 µg + Al(OH)3, n=86)	Placebo (n=79)	Nirsevimab (n=3568)	Placebo (n=3558)
Gestational age[b], weeks	**≥35 to <37:** 132 (13.3%) **≥37:** 861 (86.7%)	**≥35 to <37:** 76 (15.4%) **≥37:** 419 (84.6%)	**Mean (SD):** 32.7 (1.4) **≥29 to ≤32:** 363 (37.5%) **>32:** 606 (62.5%)	**Mean (SD):** 32.7 (1.5) **≥29 to ≤32:** 185 (38.2%) **>32:** 299 (61.8%)	**Mean (SD):** 38.8 (2.3) **<37:** 567 (14.0%) **≥37:** 3434 (85.1%) **Data missing:** 36 (0.9%)	**Mean (SD):** 38.9 weeks (5.6) **<37:** 541 (13.5%) **≥37:** 3434 (85.4%) **Data missing:** 46 (1.1%)	**Mean (SD):** 39.2 (1.0) **Median (range):** 39.1 (36.0 to 41.1)	**Mean (SD):** 38.9 (1.4) **Median (range):** 39.0 (31.4 to 41.0)	**Mean (SD):** 38.9 (1.3) **Median (range):** 39.0 (31.9 to 41.1)	**Mean (SD):** 39.0 (1.1) **Median (range):** 39.3 (34.7 to 41.3)	**Mean (SD):** 39.2 (0.9) **Median (range):** 39.2 (36.9 to 41.0)	**24 to <28:** 1 (<0.1%) **28 to <34:** 20 (0.6%) **34 to <37:** 180 (5.0%) **37 to <42:** 3343 (93.7%) **≥42:** 21 (0.6%)	**24 to <28:** 1 (<0.1%) **28 to <34:** 11 (0.3%) **34 to <37:** 157 (4.4%) **37 to <42:** 3356 (94.3%) **≥42:** 30 (0.8%)
Female sex	464 (46.8%)	257 (51.8%)	464 (48.3%)	224 (46.3%)	1950 (48.3%)	1913 (47.6%)	45 (57.0%)	39 (46.4%)	38 (49.4%)	44 (51.8%)	37 (47.4%)	1752 (49.1%)	1765 (49.6%)

	MELODY*		Griffin et al. 2020		HARMONIE		Simoes et al. 2022**					MATISSE	
	Nirsevimab (n=994)	Placebo (n=496)	Nirsevimab (n=969)	Placebo (n=484)	Nirsevimab (n=4037)	Placebo (n=4021)	Abrysvo (120 µg, n=79)	Abrysvo (120 µg + Al(OH)3, n=84)	Abrysvo (240 µg, n=78)	Abrysvo (240 µg + Al(OH)3, n=86)	Placebo (n=79)	Nirsevimab (n=3568)	Placebo (n=3558)
Weight[c]	**<5kg:** 403 (40.6%)	**<5kg:** 192 (38.7%)	**Mean (SD):** 4.60kg (1.92kg)	**Mean (SD):** 4.51kg (1.96kg)	**Mean (SD):** 6.0 (2.3) **<5kg:** 1,537 (38.1%)	**Mean (SD):** 5.9 (2.3) **<5kg:** 1,524 (37.9%)	Not reported	Not reported	Not reported	Not reported	Not reported	**≤1000g:** 1 (<0.1%) **>1000 to 1500g:** 3 (<0.1%) **>1500 to 2500g:** 177 (5.0%) **<2500g:** 3,387 (94.9%)	**≤1000g:** 2 (<0.1%) **>1000 to 1500g:** 6 (0.2%) **>1500 to 2500g:** 147 (4.1%) **<2500g:** 3,403 (95.6%)

**For MELODY, baseline characteristics were only available for the primary cohort, not the "all subjects" cohort.*

***For Simoes et al. 2022, baseline characteristics were not available for all patients included in the post-hoc efficacy analysis. The reason for the discrepancy in numbers is not clear from the published materials*

[a] *Age at baseline/injection*

[b] *Gestational age at birth was reported in slightly different ways across trials*

[c] *Weight was reported in slightly different ways across trials; for MATISSE, the weights provided are birth weights*

Abbreviations: SD= standard deviation

As mentioned above, the conceptual differences between nirsevimab and Abrysvo make comparisons across trials difficult. Gestational age at birth was generally lower in the nirsevimab trials, as these were specifically designed to include preterm infants, while the distribution of sex is roughly similar between trials.

Overall, while comparisons of the included populations are difficult, there is no evidence to indicate that the included trials are not comparable, with regards to evaluation of efficacy and safety relevant for this assessment.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	Infants (0-12 months)	Infants (0-12 months)
Gender		The model does not differentiate between male and female infants
Proportion of palivizumab-eligible infants (according to the nirsevimab trial definitions)	100 (0.17%) Based on sales estimates for palivizumab from Medstat.dk	100 (0.17%) Based on sales estimates for palivizumab from Medstat.dk
Proportion of healthy pre-term infants[a]	1,545 (2.64%)	1,545 (2.64%)
Proportion of healthy term infants[b]	56,784 (97.18%)	56,784 (97.18%)

[a] *Born at or before 34+6 wGA, not eligible for palivizumab*
[b] *Defined as infants born at or after 35 wGA, not eligible for palivizumab*

Source: data on gestational age from eSundhed.dk (2023)[90]

6.1.4 Efficacy – results per MELODY

MELODY was a phase 3, randomised, double-blind, placebo-controlled trial, in which healthy late preterm and term infants (with a GA over 35+0 weeks) were randomised to either nirsevimab or placebo[99] The efficacy results from MELODY are presented below:

Table 11. Efficacy results from MELODY (All subjects)

Outcome	Intervention	n	Cases (%)	Relative efficacy
Number of Participants with MA RSV LRTI Through 150 Days Post Dose	Nirsevimab	2009	24 (1.2%)	Relative risk reduction: 76.4% (95% CI: 62.3% to 85.2%) P-value: <0.0001
	Placebo	1003	54 (5.4%)	
Number of Participants with MA RSV LRTI With	Nirsevimab	2009	9 (0.4%)	Relative risk reduction: 76.9% (95% CI: 49.4% to 89.4%) P-value: 0.0002

Hospitalisation Through 150 Days Post Dose	Placebo	1003	20 (2.0%)

Abbreviations: CI= confidence interval, LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus
Notes: P-values and 95%CI were estimated with Poisson regression with robust variance (including stratification factors [age at randomisation as covariate) obtained after multiple imputation.
Source: clinicaltrials.gov (NCT03979313)

6.1.5 Efficacy – results per Griffin et al. 2020

Griffin et al. 2020 was a phase 2b, randomised, double-blind, placebo-controlled trial, in which healthy preterm infants (with a GA between 29+0 and 34+6 weeks) were randomised to either nirsevimab or placebo.[84] Of note, all included infants received the lower dose of 50 mg dose meaning no adjustment for weight as per approved dosing. The efficacy results from Griffin et al. 2020 are presented below:

Table 12. Efficacy results from Griffin et al. 2020

Outcome	Intervention	n	Cases (%)	Relative efficacy
Number of Participants With MA RSV Confirmed LRTI	Nirsevimab	969	25 (2.6%)	Relative risk reduction: 70.1% (95% CI: 52.3% to 81.2%) P-value: <0.0001
	Placebo	484	46 (9.5%)	
Number of Participants Hospitalized Due to RSV confirmed LRTI	Nirsevimab	969	8 (0.8)	Relative risk reduction: 78.4% (95% CI: 51.9% to 90.3%) P-value: 0.0002
	Placebo	484	20 (4.1)	

Abbreviations: CI= confidence interval, LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus
Notes: P-values and 95%CI were estimated with Poisson regression.
Source: clinicaltrials.gov (NCT02878330)

6.1.6 Efficacy – results per HARMONIE

HARMONIE is a phase 3b, randomised, open-label trial in which healthy term and preterm infants (with a GA above 29 weeks) were randomised to either nirsevimab or standard care (i.e., no intervention)[9]. The study is ongoing, but efficacy results are available and are presented below.

Table 13. Efficacy results from HARMONIE

Outcome	Intervention	n	Cases (%)	Relative efficacy
Hospitalization for RSV-associated LRTI	Nirsevimab	4037	11 (0.3%)	Efficacy: 83.2% (95% CI: 67.8% to 92.0%)
	Placebo	4021	60 (1.5%)	
Very severe RSV-associated LRTI (defined as hospitalisation for RSV-associated with an oxygen saturation <90%)	Nirsevimab	4037	5 (0.1%)	Efficacy: 75.7% (95% CI: 32.8 to 92.9%)
	Placebo	4021	19 (0.5%)	

Abbreviations: CI= confidence interval, LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus
Notes: Efficacy was calculated using the exact method with binomial distribution.
Source: Drysdale et al. 2023[9]

6.1.7 Efficacy – results per Simoes et al. 2022

Simoes et al. 2022 was a phase 2b, randomised, placebo-controlled, observer-blinded trial, in which pregnant healthy women were randomised to vaccination with Abrysvo or placebo. Vaccination was administered between 24 and 36 weeks of gestation. Efficacy outcomes for the infants born to the randomised women are presented in Table 14 below (efficacy analyses were post-hoc and the timing of assessment was not clearly reported, so results should be interpreted with caution):

Table 14. Efficacy outcomes from Simoes et al. 2022

Outcome	Intervention	n	Cases (%)	Relative efficacy
MA LRTI associated with RSV (post-hoc analysis)	Abrysvo	405	3 (0.7%)	Relative risk reduction: 84.7% (95% CI: 21.6% to 97.6%)
	Placebo	103	5 (4.9%)	
Severe MA LRTI associated with RSV (post-hoc analysis)	Abrysvo	405	1 (0.2%)	Relative risk reduction: 91.5% (95% CI: −5.6% to 99.8%)
	Placebo	103	3 (2.9%)	

Abbreviations: CI= confidence interval, LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus
Notes: The efficacy was calculated as the relative risk reduction in the combined Abrysvo groups compared with the placebo group. Confidence intervals were calculated with the use of an exact conditional method based on binomial distribution. Efficacy analyses were not preplanned, and as such were post-hoc.
Source: Simoes et al. 2022[10]

6.1.8 Efficacy – results per MATISSE

MATISSE was a phase 3, randomised, double-blind, placebo-controlled trial in which healthy women with uncomplicated pregnancies were randomised to vaccination with Abrysvo or placebo. Vaccination was administered between 24 and 36 weeks of gestation. MATISSE reported efficacy at 90, 120, 150, and 180 days post birth; to allow for comparison with nirsevimab, efficacy data for 150 days post birth is presented here. Efficacy outcomes for the infants born to the randomised women are presented in Table 15 below:

Table 15. Efficacy results from MATISSE

Outcome	Intervention	n	Cases (%)	Relative efficacy
MA LRTI associated with RSV (150 days post dose)	Abrysvo	3495	47 (1.3%)	Vaccine efficacy: 52.5% (95% CI: 28.7% to 68.9%)
	Placebo	3480	99 (2.8%)	
Severe MA LRTI associated with RSV (150 days post dose)	Abrysvo	3495	16 (0.5%)	Vaccine efficacy: 70.9% (44.5% to 85.9%)
	Placebo	3480	55 (1.6%)	
RSV-associated hospitalisations (150 days post dose)	Abrysvo	3495	17 (0.5%)	Vaccine efficacy: 56.4% (5.2% to 81.5%)
	Placebo	3480	39 (1.1)	

Abbreviations: CI= confidence interval, LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus
Notes: The efficacy was calculated as the relative risk reduction in the combined Abrysvo groups compared with the placebo group. Confidence intervals were calculated with the use of an exact conditional method based on binomial distribution.
Source: Kampmann et al. 2023[3]

6.1.9 Efficacy – Palivizumab

The clinical efficacy of palivizumab in the prevention of RSV hospitalisations was sourced from a 2021 Cochrane review[6]. The review included five studies comparing palivizumab with placebo; the five studies included a total of 3,343 patients[6].

Blanken et al. (2013)[100], randomised 429 healthy preterm infants (GA between 32 to 35) to receive either palivizumab (214) or a placebo (215). After one year, 2 (0.9%) patients in the palivizumab arm were hospitalized versus 11 (5.1%) patients in the placebo arm (RR: 0.18, 95% CI: 0.04 to 0.81)

Tavsu et al. (2014)[101] ref, randomised 83 infants born before week 32 GA, to receive either palivizumab (41) or no intervention (42). Infants were followed up for 2 RSV seasons. In the palivizumab group, no cases of hospitalization due to RSV were registered, while in the control group 10 (24.4%) cases were registered at 2 years of follow up. (RR: 0.5, 95% CI: 0.00 to 0.81)

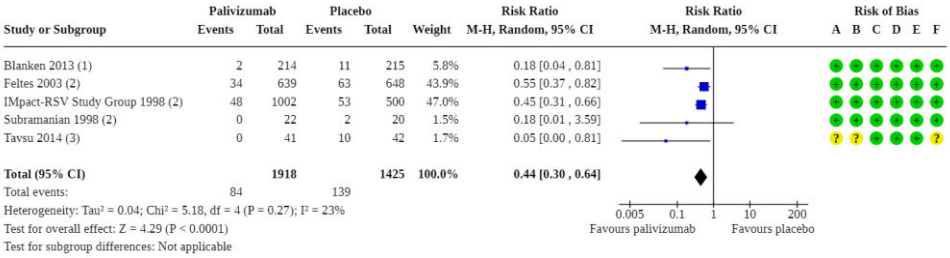
One study (IMpact-RSV) randomised 1,502 infants who were either born before week 35 of gestation (≤ 35 weeks GA) or had bronchopulmonary dysplasia to receive either palivizumab or placebo. Researchers found that in the palivizumab group, 48 out of 1002 infants were hospitalised with RSV, versus 53 out of 500 infants in the placebo group (RR: 0.45, 95% CI: 0.31 to 0.66)[94].

Another study, (Subramanian et al. 1998), randomised 42 infants who were born before week 35 of gestation (≤ 35 weeks GA) and were less than 6 months old, or infants with bronchopulmonary dysplasia of less than 24 months old, to receive either palivizumab or placebo. None of the 20 infants randomised to palivizumab group were hospitalised with RSV versus two out of 22 in the placebo group (RR: 0.18, 95% CI: 0.01 to 3.59)[102].

The final study randomised 1,287 infants less than 2 years old with haemodynamically significant heart disease to either palivizumab or placebo. In the palivizumab group, 34 out of 369 infants were hospitalised with RSV versus 63 out of 648 in the placebo group (RR: 0.55, 95% CI: 0.37 to 0.82)[103].

The five studies were combined in a fixed-effects meta-analysis. Low statistical heterogeneity was observed (I^2 = 23%) and the meta-analysis resulted in a RR of 0.44 (95% CI: 0.30 to 0.64) for palivizumab versus placebo in high risk infants (see[104]).

Figure 3. Forest plot for meta-analysis of palivizumab versus placebo - RSV Hospitalisation



Source: [6]

6.1.10 Effectiveness – results from real world evidence

Nirsevimab was already implemented in certain countries and regions during the past season, 2023/24, all with a strategy to protect all infants from RSV with nirsevimab. Sanofi has supplied two million doses to these programmes. Publications based here on real-world have come out in recent months and are briefly described below. Of note, while the studies themselves were identified in the SLR, several publications were published after the searches were conducted.

Effectiveness for reduction in hospitalizations based on case-controlled studies of an all-infants programme ranged from 84% to 90% in a Spanish region and the USA, respectively. Using a test-negative design from two Spanish region resulted in an effectiveness of 70%[105]. Reductions in hospitalizations of an all-infants group compared to previous seasons were reported from Luxembourg [97] and Galicia[106] and ranges from 69% to 89%.

Importantly a high acceptance of nirsevimab was seen in all countries as a driver of the pronounced reduction in number of hospitalizations. In countries with an all-infant programme, coverage rates between 84% and 99% [105] were achieved. Slightly higher coverage was reported for infants who were given nirsevimab at birth compared to infants born before the season.

7. Comparative analyses of efficacy

This application considers four clinical questions; the methods and results for each clinical question are presented below.

7.1 What is the effect of nirsevimab versus palivizumab in infants who are candidates for palivizumab treatment?

No trials examining the efficacy of nirsevimab in infants who are candidates for palivizumab treatment have been identified. Therefore, a conservative assumption of non-inferiority has been made; although pharmacokinetic and bioavailability data from the MEDLEY trial indicate that the effect in these infants is likely similar to the effect observed in pre-term and term infants[81].

7.2 What is the effect of nirsevimab versus placebo in preterm infants (born prior to week 35 of gestational age)

The effect of nirsevimab versus placebo in preterm infants was investigated in the Griffin et al. 2020[84] and HARMONIE[107] studies.

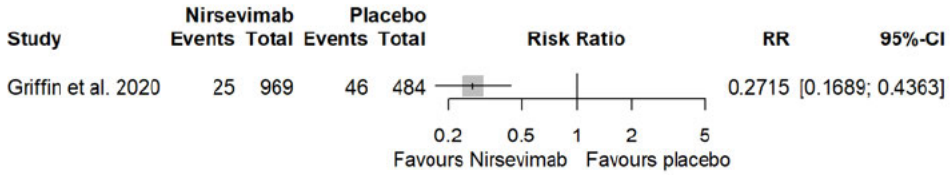
The outcome of medically attended RSV-associated lower respiratory tract infection was only included in Griffin et al. 2020, whereas the outcome of RSV-associated hospitalisation was included in both Griffin et al. 2020 and HARMONIE.

7.2.1 Medically attended RSV-associated lower respiratory tract infection

The results for infants born prior to week 35 of gestational age in Griffin et al. 2020 are shown in Figure 4. Nirsevimab led to a statistically significant reduction in RSV MA-LRTIs

at 150 days post-randomisation, with a RR of 0.2715 (95% CI: 0.1689 to 0.4363) which corresponds to a vaccine effectiveness of 72.85% (95% CI: 56.37% to 83.11%).

Figure 4. Results from Griffin et al. 2020 for the outcome of RSV MA-LRTIs (150 days post-randomisation)



Abbreviations: RR, relative risk; CI, confidence interval

7.2.2 RSV-associated hospitalisations

As mentioned above, RSV-associated hospitalisations were investigated in both Griffin et al. 2020 and HARMONIE. The definitions of the outcome were the same in both trials and the trial's methodologies was generally comparable. However, for the HARMONIE trial, data was only available for infants born prior to week 37 of gestational age, therefore this data was used as a proxy for data from infants born prior to week 35 of gestational age. Overall, the studies were considered similar enough for inclusion in a meta-analysis.

Therefore, a random-effects meta-analysis was conducted, using the *metabin* from the *meta* package in R. The defaults settings of the *metabin* package were used, meaning that in the random-effects meta-analysis the Mantel-Haenszel estimator is used in the calculation of the between-study heterogeneity, which is then used in the DerSimonian-Laird estimator. The random-effects estimate is based on the inverse variance method.

A summary of the studies included in the meta-analysis are shown in Table 16.

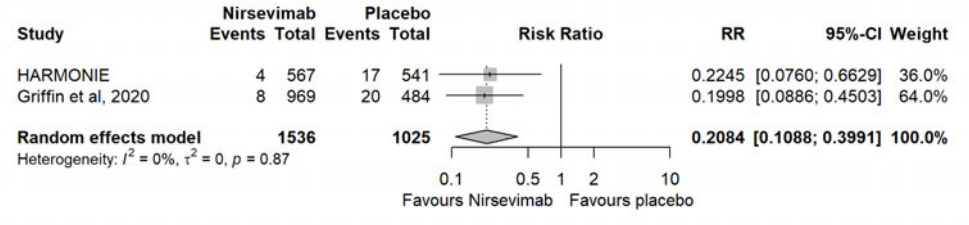
Table 16. Trials included in the meta-analysis for RSV-associated hospitalisation (<35 wGA)

Study ID	Population	Interventions	Event counts, n (%)
Griffin et al. 2020[84]	Infants born between week 29 + 0 and week 34 + 6 of gestational age	Nirsevimab (n = 969) Placebo (n = 484)	Nirsevimab = 8 (0.83%) Placebo = 20 (4.13%)
HARMONIE[9]	Infants born between week 29+0 and week 36+6 of gestational age	Nirsevimab (n = 567) No prophylaxis (n = 541)	Nirsevimab = 4 (0.70%) No prophylaxis = 17 (3.14%)

Abbreviations: GA, gestational age

The results of the random-effects meta-analysis are shown in Figure 5. Nirsevimab led to a statistically significant reduction in RSV-associated hospitalisations 150 days post-randomisation when compared to no prophylaxis (or placebo) with a RR of 0.2084 (95% CI: 0.1088 to 0.3991) corresponding to a vaccine efficacy of 79.16% (95% CI: 60.09% to 89.12%). No statistical heterogeneity was identified, with a I^2 of 0%.

Figure 5. Results of meta-analysis of nirsevimab versus placebo for the outcome of RSV MA-LRTIs (150 days post-randomisation, <35 wGA)



Abbreviations: RR, relative risk; CI, confidence interval

7.3 What is the effect of nirsevimab versus placebo in term infants (born after or in week 35 of gestational age)

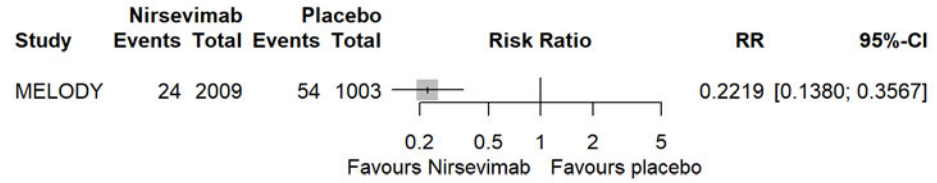
The effect of nirsevimab versus placebo in preterm infants was investigated in the MELODY[99] and HARMONIE[107] trials.

The outcome of medically attended RSV-associated lower respiratory tract infection was only included in MELODY, whereas the outcome of RSV-associated hospitalisation was included in both MELODY and HARMONIE.

7.3.1 Medically attended RSV-associated lower respiratory tract infection

The results for infants born in or after week 35 of gestational age in MELODY are shown in Figure 6. Nirsevimab led to a statistically significant reduction in RSV MA-LRTIs at 150 days post-randomisation, with a RR of 0.2219 (95% CI: 0.1380 to 0.3567) corresponding to a vaccine effectiveness of 77.81% (95% CI: 64.33% to 86.20%).

Figure 6. Results from MELODY for the outcome of RSV MA-LRTIs (150 days post-randomisation)



Abbreviations: RR, relative risk; CI, confidence interval

7.3.2 RSV-associated hospitalisations

As outlined above, the outcome of RSV-associated hospitalisations was included in both the MELODY and HARMONIE trials; however, from the HARMONIE trial, data was only available for infants born in or after week 37 of gestational age. Therefore, this data was used as a proxy for data from infants born in or after week 37 of gestational age. Overall, the studies were considered similar enough for inclusion in a meta-analysis.

The methods used for the meta-analysis were the same as described in section 7.2.2.

A summary of the included trials is provided in Table 17.

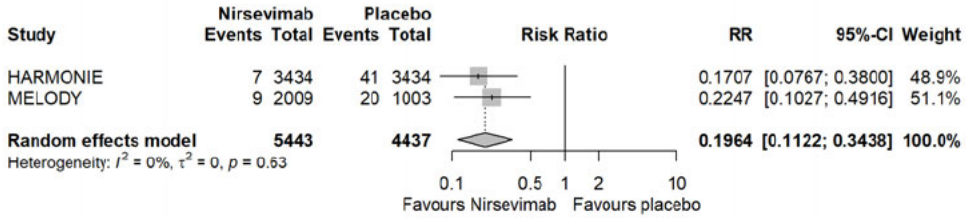
Table 17. Trials included in the meta-analysis for RSV-associated hospitalisation (>=35 wGA)

Study ID	Population	Interventions	Event counts, n (%)
HARMONIE[9]	Infants born in week 37 of gestational age or later	Nirsevimab (n = 3434) No prophylaxis (n = 3434)	Nirsevimab = 7 (0.20%) No prophylaxis = 41 (1.19%)
MELODY[99]	Infants born in week 35 of gestational age or later	Nirsevimab (n = 2009) Placebo (n = 1003)	Nirsevimab = 9 (0.45%) Placebo = 20 (1.99%)

Abbreviations: GA, gestational age

The results of the random-effects meta-analysis are shown in Figure 7. Nirsevimab led to a statistically significant reduction in RSV-associated hospitalisations when compared to no prophylaxis (or placebo) with a RR of 0.1964 (95% CI: 0.1122 to 0.3438) corresponding to a vaccine efficacy of 80.36% (95% CI: 65.62% to 88.78%). No statistical heterogeneity was identified, with a I^2 of 0%

Figure 7. Results of meta-analysis of nirsevimab versus placebo for the outcome of RSV MA-LRTIs (150 days post-randomisation, >=35 wGA)



Abbreviations: RR, relative risk; CI, confidence interval

7.4 What is the effect of nirsevimab versus Abrysvo in term infants (born after or in week 35 of gesational age)

To facilitate the comparison of the efficacy of nirsevimab versus Abrysvo in the prevention of RSV infections in infants, a frequentist NMA was carried out, using the efficacy data from the relevant studies described in section 6.

7.4.1 Differences in definitions of outcomes between studies

The efficacy outcomes included in the comparative analysis are provided in Table 18 below.

Table 18. Definitions of outcomes included in the comparative analysis of nirsevimab versus Abrysvo

Outcome	Nirsevimab trials		Abrysvo trials	
	Outcome definition	Time-points	Outcome definition	Time-points
RSV MA-LRTI	Medically attended RSV infection (confirmed by RT-PCR), with the presence of signs of	150 days post dose	A medically attended visit, signs of lower respiratory tract	90, 120, 150, 180, and 360 days after birth (for MATISSE, in Simoes et al.

	lower respiratory tract disease, and the presence of signs of severe respiratory disease		disease, and a positive RT-PCR results for RSV	2022, the time-point for the post-hoc efficacy analysis was unclear)
RSV Hospitalisations	RSV MA-LRTI with hospitalisation	150 days post dose	RSV MA-LRTI with hospitalisation	90, 120, 150, 180, 210, 240, 270, and 360 days after birth

Abbreviations: LRTI= lower respiratory tract infection, MA= medically attended, RSV= respiratory syncytial virus, RT-PCR= reverse transcription polymerase chain reaction.

Overall, the outcome definitions for the trials included in the comparative analysis are very similar and allow for an indirect treatment comparison. While outcome data for multiple time-points was available for the Abrysvo trials, the nirsevimab trials only examined efficacy after 150 days post dose; thus, analyses were only conducted for this time-point.

7.4.2 Method of synthesis

A brief description of the methods used for the frequentist NMA of nirsevimab versus Abrysvo is provided below. Details on the methods used are available in Appendix C.

For each of the included outcomes (RSV MA-LRTI and RSV-associated hospitalisation), the total number of patients and the number of cases was extracted from all relevant trials, which allowed for calculation of risk-ratios of nirsevimab and Abrysvo versus placebo/no intervention. These risk ratios were then combined in a frequentist random-effects NMA using the *netmetabin* function from the *netmeta* package in R.[108] The treatment network of the NMA and details on the methods of synthesis are provided in Appendix C. Details on the studies included in the various analyses are also provided in Appendix C.

7.4.3 Included trials

The clinical efficacy of nirsevimab versus placebo in term infants was informed by the MELODY[99] and HARMONIE[107] trials, as described in section 7.3. The efficacy of Abrysvo against placebo was investigated in the Simoes et al. 2022[109] and MATISSE[3] trials; however, in both trials women were vaccinated between week 24 and week 36 of gestation. While timing of vaccination was not a pre-specified subgroup criterion and the results have not been published in a peer-reviewed journal, data from the MATISSE trial included in the EPAR for Abrysvo, indicates a larger effect on the outcome of MA RSV-LRTI in women vaccinated after week 28[110]. As a potential vaccination in Denmark would likely occur around week 32; data from women vaccinated after week 28 was used for this outcome. No efficacy data stratified by vaccination timing was available for the outcome of RSV-hospitalisation.

A summary of the trial included in the NMAs for MA RSV-LRTI and RSV-associated hospitalisations is shown in Table 19 and Table 20, respectively.

Table 19. Trials included in the network meta-analysis for RSV-associated hospitalisation

Study ID	Population	Interventions	Event counts, n (%)

MELODY[99]	Infants born in week 35 of gestational age or later	Nirsevimab (n = 2009) Placebo (n = 1003)	Nirsevimab = 24 (1.19%) Placebo = 54 (5.38%)
MATISSE[4]	Infants born to healthy women (excluding women vaccinated prior to 28 wGA)	Abrysvo (n = 2605) Placebo (n = 2614)	Abrysvo = 18 (0.69%) Placebo = 76 (2.91%)

Table 20. Trials included in the network meta-analysis for RSV-associated hospitalisation

Study ID	Population	Interventions	Event counts, n (%)
MELODY[99]	Infants born in week 35 of gestational age or later	Nirsevimab (n = 2009) Placebo (n = 1003)	Nirsevimab = 9 (0.45%) Placebo = 20 (1.99%)
HARMONIE[107]	Infants born in week 37 of gestational age or later	Nirsevimab (n = 3434) No prophylaxis (n = 3434)	Nirsevimab = 7 (0.20%) No prophylaxis = 41 (1.19%)
MATISSE[3]	Infants born to healthy women (regardless of vaccination timing)	Abrysvo (n = 3495) Placebo (n = 3480)	Abrysvo = 17 (0.49%) Placebo = 39 (1.12%)

7.4.4 Results from the comparative analysis

An overview of the results from the NMA of nirsevimab is presented in Table 21.

Table 21 Results from the random effects NMA of nirsevimab vs. Abrysvo for prevention of RSV in infants

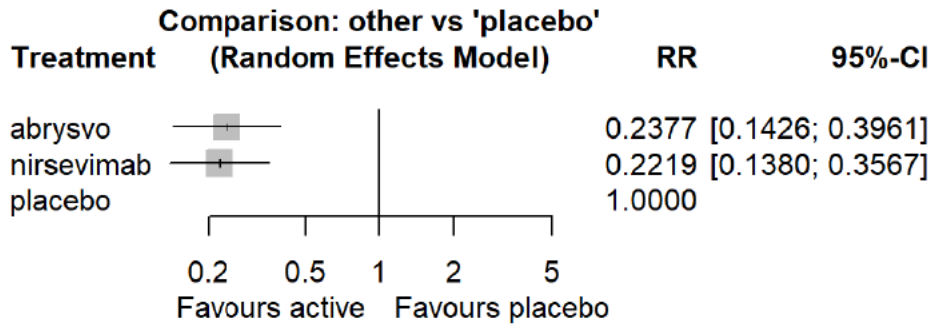
Outcome measure	Nirsevimab vs placebo, RR (95% CI)	Abrysvo vs placebo, RR (95% CI)	Nirsevimab vs Abrysvo, RR (95% CI)
RSV MA-LRTI, 150 days post dose or post birth	0.222 (0.138 to 0.357) P-value: <0.0001	0.238 (0.143 to 0.396) P-value: <0.0001	0.934 (0.465 to 1.875) P-value: 0.8470
RSV hospitalisations, 150 days post dose or post birth	0.196 (0.112 to 0.344) P-value: <0.0001	0.434 (0.246 to 0.766) P-value: 0.040	0.453 (0.204 to 1.005) P-value: 0.0513

Abbreviations: RR= Risk ratio, CI= confidence interval, MA= medically attended, LRTI= lower respiratory tract infections, RSV= Respiratory syncytial virus

7.4.5 Efficacy – results per medically attended lower respiratory tract infection caused by respiratory syncytial virus

In the NMA, both nirsevimab and Abrysvo were significantly superior to placebo (or no intervention), with RRs of 0.222 (95% CI: 0.138 to 0.357) and 0.238 (95% CI: 0.143 to 0.396) respectively (see Figure 8). This corresponds to a vaccine efficacy of 76.23% and 77.81% for nirsevimab and Abrysvo, respectively.

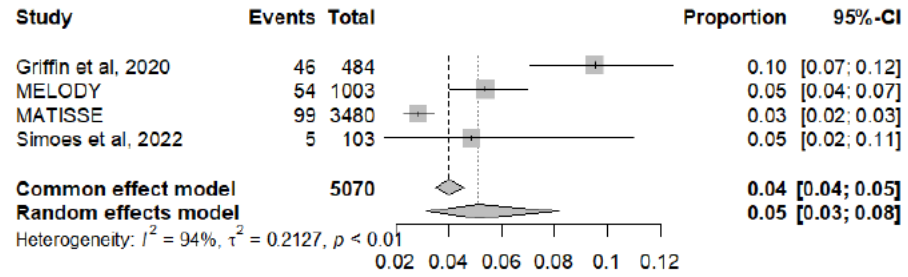
Figure 8. Results from NMA; MA RSV-LRTI (150 days post dose/birth)



Nirsevimab was numerically superior to Abrysvo with a RR of 0.934; however, the difference was not statistically significant, with the 95% CI containing values indicating that either treatment may be clinically significantly superior to the other.

To obtain estimates of absolute effects, a measure of baseline risk of RSV MA-LRTI in all included trials was obtained by synthesising the risk observed in the placebo arm of all studiesa random-effects meta-analysis (regardless of timing of birth and vaccination, see Figure 9).

Figure 9. Random effects meta-analysis of RSV MA-LRTI risk in placebo arms



The relative effect estimates for nirsevimab and Abrysvo obtained through the NMA were then applied to this baseline risk. The estimated absolute effect of nirsevimab and Abrysvo, as well as the number needed to vaccinate, compared to placebo are shown in Table 22.

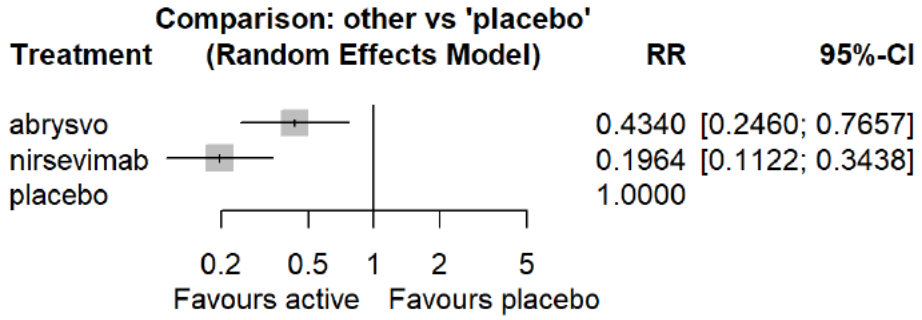
Table 22. Absolute effect estimates obtained from the NMA of RSV MA-LRTI

Treatment	Absolute risk	Absolute difference relative to placebo	Number needed to vaccinate
Placebo	5.38%	N/A	N/A
Nirsevimab	1.19%	4.19%	23.86
Abrysvo	1.28%	4.1%	24.12

7.4.6 Efficacy – results per RSV-associated hospitalisation

Both nirsevimab and Abrysvo were significantly superior to placebo (or no intervention), with RRs of 0.198 (95% CI: 0.13 to 0.302) and 0.434 (95% CI: 0.246 to 0.766) respectively (see Figure 10).

Figure 10. Results from NMA; RSV-associated hospitalisation (150 days post dose/birth)

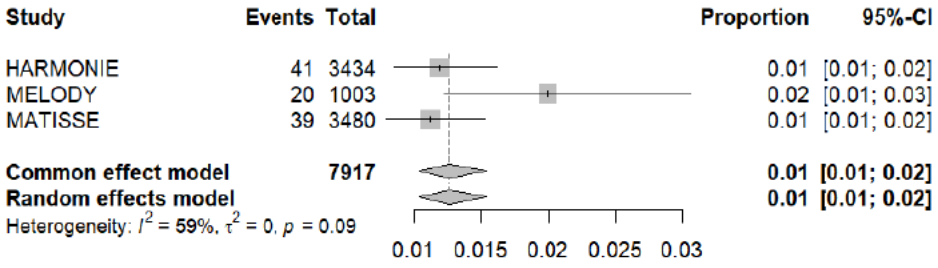


Abbreviations: RR, relative risk; CI, confidence interval

For RSV-associated hospitalisation, nirsevimab was numerically superior to Abrysvo with a RR of 0.453 (95% CI: 0.204 to 1.004). The difference was borderline statistically significant (i.e., the p-value was 0.0513). The difference between nirsevimab and Abrysvo corresponds to a 54.7% relative risk reduction for RSV-associated hospitalisation.

To obtain estimates of absolute effects, the same approach described above was utilised. The results of the meta-analysis of risk in the placebo arm are shown in Figure 11 and the absolute effect estimates are shown in Table 23.

Figure 11. Random effects meta-analysis of RSV hospitalisation risk in placebo arms



Abbreviations: CI, confidence interval

Table 23. Absolute effect estimates obtained from the NMA of RSV hospitalisations

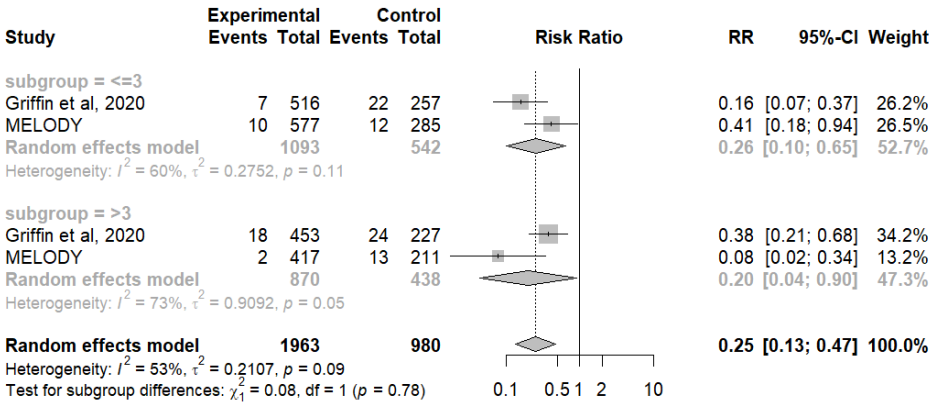
Treatment	Absolute risk	Absolute difference relative to placebo	Number needed to vaccinate
Placebo	1.88%	N/A	N/A

Nirsevimab	0.37%	1.51%	66.22
Abrysvo	0.82%	1.06%	94.34

7.5 Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation

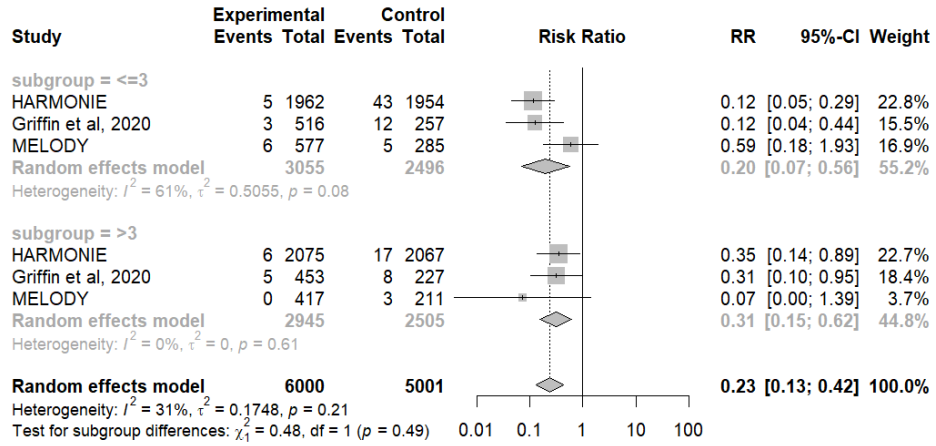
Figure 12 and Figure 13 shows results of a subgroup analysis comparing infants of <= 3 months of age at randomisation with those of > 3 months of age at randomisation in the nirsevimab trials for the outcomes of MA RSV-LRTI and RSV-associated hospitalisation respectively. Data stratified by both age at randomisation and gestational age at birth was not available, so the analyses presented below are based on the ITT populations of the included trials.

Figure 12. Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation (MA RSV-LRTI)



Abbreviations: RR, relative risk; CI, confidence interval

Figure 13. Subgroup analysis for nirsevimab versus placebo stratified by age at randomisation (RSV-associated hospitalisation)



Abbreviations: RR, relative risk; CI, confidence interval

As shown, while the effect in the MELODY trial was lower in children of <= 3 months of age at randomisation, when considering the totality of the evidence, there is no indication that age acts as an effect modifier for nirsevimab.

7.6 Efficacy conclusions and interpretation

As described above, both nirsevimab and Abrysvo are statistically significantly superior to placebo (or no intervention) in preventing RSV-LRTI and RSV-hospitalisations. Additionally, in a random-effects NMA nirsevimab was superiorto Abrysvo in preventing RSV hospitalisations.

RSV in infants poses a major challenge for the Danish healthcare system; RSV hospitalisations are especially burdensome, with pediatric departments often being at or above maximum capacity during the RSV season and based on feedback from Danish clinicians about half of all hospital admissions in pediatric departments during the winter season are associated with RSV. During the 2023/24 season, 1402 infants under one year of age were hospitalised with lab-confirmed RSV, of these, 939 (67.2%) occurred within a 7-week period (week 47/2023 to week 1/2024)[44].

Prevention of RSV and RSV-related adverse health events will clearly lead to increased benefits for the individual infant and their families by preventing morbidity, hospitalisations, potential sequalae, and associated stress/concerns. Equally important, prevention of RSV infections can ease the pressure on the healthcare system, freeing up capacity for other treatments that might require not only hospitalisation but also mechanical ventilation, and ICUs.

While the benefits are quantifiable using the reduced number of infections as a proxy for healthcare resource usage, the concrete consequences of RSV prevention outside the infants QALY spectrum and the healthcare costs are harder to grasp. Nonetheless, research shows that paediatricians with high work-related stress were compromised in

terms of quality of care[111]. These findings emphasize once again the importance of system-wide pressure and professionals' burnouts, especially in seasonal diseases such as RSV.

In the base-case scenario of the health economic model, nirsevimab prevents 1,008 hospitalisations relative to SoC and 461 hospitalisations relative to maternal immunisation with Abrysvo. Importantly, the hospitalisations avoided by RSV prevention are not uniformly distributed across the year; rather the avoided hospitalisations happen during the RSV season, where the stress on the health care system is at its highest.

The number of adverse health events under each modelled strategy (SoC, maternal immunisation, and nirsevimab) as well as the differences between nirsevimab and SoC and Abrysvo are shown in Table 24.

Table 24. Adverse health events under each scenario and number of prevented events with nirsevimab relative to SoC and Abrysvo – from the health economic model, base case settings.

Health event	Standard of care	Abrysvo	Nirsevimab	Prevented with nirsevimab relative to standard of care	Prevented with nirsevimab relative to Abrysvo
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infants receiving Intensive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infants receiving mechanical ventilation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pediatric emergency admission visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Efficacy for either strategy (Nirsevimab, Abrysvo, and SoC (prophylaxis for high risk, BSC for non-high risk) is based on inputs such as prevention efficacy, protection waning, and coverage rate.

The efficacy of prophylaxis is defined as the reduction in RSV MA-LRTIs in the inpatient and outpatient settings. The model allows the prevention efficacy inputs to be used as either a single value for the overall population or specific values for each of the three subpopulations. If the analysis considers the overall population, the efficacy of each

prophylaxis is assumed to be the same across the infant subpopulations – an assumption that is not considered clinically feasible.

The efficacy of nirsevimab in the preterm and term populations is obtained from the NMA of nirsevimab versus no intervention and Abrysvo, described in section 7. Due to the mechanism of action and pharmacokinetic data of nirsevimab, its efficacy is not expected to differ between preterm and term infant subpopulations entering their first RSV season. This assumption is based on the results of pivotal studies investigating nirsevimab designed to include all infants when examined together, and consistent levels of efficacy were demonstrated across the population subpopulations (i.e., preterm vs. term) and the spectrum of disease severity. Based on the results of the phase II/III MEDLEY trial, nirsevimab is assumed to be non-inferior to palivizumab in terms of protection against RSV MA-LRTIs in the palivizumab-eligible population.[75]

The efficacy of Abrysvo for the prevention of RSV in infants is examined in two trials. Simoes et al. 2022 (a phase 2b trial) reported the vaccine efficacy in preventing the outcomes of any RSV-associated LRTI and severe RSV-associated LRTI via a post-hoc analysis[10,112]. In MATISSE, a phase 3 trial, 3495 infants were born to mothers vaccinated with Abrysvo and 3480 infants were born to mothers that had received a placebo[3,113,114].

8.1.1 Extrapolation of efficacy data

Table 25 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
NA	NA

Abbreviations: NA= not applicable or not available

8.1.2 Calculation of transition probabilities

NA

Table 26 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
NA	NA	NA	NA

Abbreviations: NA= not applicable or not available

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

NA

8.4 Other assumptions regarding efficacy in the model

As outlined in section 3.3.1, in Denmark, palivizumab is recommended for infants born before week 32 and 0 days with lung disease, or children born at any time with certain lung and heart diseases, as described in the Danish guidelines for RSV prevention[2]. To the

best of our knowledge, no data on the number of palivizumab-eligible infants in Denmark is available but based on number of doses per infant and sales estimates for palivizumab from medstat.dk the number is likely around a 100 infants per year. Assumptions regarding model inputs and functionality are described in Table 27.

Table 27. Assumptions and inputs used in the base case in the health economic model

Parameter / Input	Assumption or source	Rationale
Total number of annual births and distribution of births by month	Data from Statistics Denmark, 2024[89].	Most up to date data for the Danish population
Proportion of infants belonging to the three different sub-populations	Palivizumab-eligible: Set to 100 infants, based on sales estimates for palivizumab. Preterm infants: all infants born prior to week 35+0 of gestational age, minus the 100 palivizumab-eligible. Term infants: all infants born at or after week 35+0 of gestational age. Data on gestational age at birth by week obtained from eSundhed.dk, 2023[90].	The number of palivizumab-eligible infants is an estimation, based on sales. The distribution of births by gestational age are based on the most up to date data for the Danish population
Monthly probability of RSV infections (as percentage of total infections)	Data on distribution of RSV infections in the 2023/24 season from SSI[44].	Most up to date data for the Danish population. Aggregation across seasons would lead to "blurring" of both length and intensity of seasons.
Start and duration of RSV season	Start of season: November Length of season: 4 months	Visual inspection of the monthly probabilities of RSV infections
Timing of nirsevimab administration	Infants born within season are administered nirsevimab at birth Infants born outside of the season are administered nirsevimab at the start of season (in a "catch-up programme).	This approach allows for full protection for all infants during the RSV season
Timing of maternal immunisation with Abrysvo	All pregnant women are immunised with Abrysvo in week 32 of gestation.	[redacted]

Efficacy and length of protection – palivizumab	**Relative risk reduction** Palivizumab eligible infants: 56%	The efficacy of palivizumab is obtained from a 2021 Cochrane review.[6]
Efficacy and length of protection - nirsevimab	**Relative risk reduction:** Palivizumab eligible infants: 56% Preterm infants: 79.16% Term infants: 80.36 Length of protection: 5 months	For the palivizumab-eligible population, the relative risk reduction is set to match that of palivizumab, to maintain non-inferiority. The relative risk reduction for the term and preterm population is obtained from the comparison between nirsevimab and placebo in the NMA (see section 7). The length of protection is based on the clinical studies of nirsevimab, where efficacy was evaluated after 150 days.
Efficacy and length of protection - Abrysvo	Relative risk reduction: 56.6% Length of protection: 6 months	The relative risk reduction is obtained from the comparison between Abrysvo and placebo in the NMA (see section 7). The length of protection of 6 months is based on the SMPC for Abrysvo, which states that Abrysvo offers protection from birth through 6 months of age.[4] *Note: the efficacy of Abrysvo is derived from the NMA, which used the 150 days post birth timepoint – efficacy at 180 days is slightly lower, but to ensure consistency in results the former was used. This is a conservative assumption.*
Time required for antibody transfer for Abrysvo	100% antibody transfer after two weeks.	While clinical evidence suggests that 100% antibody transfer takes longer than two weeks, it is assumed that the full efficacy of maternal immunisation with Abrysvo is achieved if ≥ 2 weeks pass between vaccination and birth. This is a conservative assumption.
Waning of efficacy	No waning of efficacy is modelled for either intervention.	For nirsevimab, clinical efficacy was evaluated 150 days post dose; while some effect after this time-point is plausible, the conservative assumption of no waning was made to avoid assumptions of efficacy with no supporting data.

		For Abrysvo, the SMPC states that infants are protected from birth through 6 months of age.[4]
Coverage rate - nirsevimab	Term infants: 80% Pre-term infants: 80% Palivizumab-eligible infants (per model definition): 80%	Nirsevimab programmes have achieved coverage rates > 80% in Luxembourg (84%)[97] and Spain (91.7%)[98]. Based on clinician feedback, the very high coverage rates in Spain were due to a very intensive promotion campaign, and may not be achievable in Denmark, thus a conservative estimate of coverage of 80% was chosen.[97]
Coverage rate – Abrysvo	Term infants: 70% Pre-term infants: 21.5% Palivizumab-eligible infants: 0%	The coverage rate of 70% is based on the average coverage rate of the Danish pertussis maternal immunisation programme in the 2023/24 season[48]. The influenza and covid-19 maternal immunisations programmes have lower coverage, with 13% for covid-19 and 27% for influenza in the 2022/23 season[115] [redacted] The 21.5% for the pre-term infants, are used to adjust for the fact that only 30% of the pre-term population will be born after week 34+0[90] and thus have achieved antibody transfer. This approach means that infants immunised in week 32 but born prior to week 34 are not incurring costs of vaccination, which is a conservative approach.
Risk of RSV hospitalisations	Hospitalisation rates for all infants aged 0-5 months and 6-11 months from the 2021/22 to 2023/24 seasons are obtained from the RSV Dashboard published by Statens Serum Institut. These rates are then distributed across month of age using data on the distribution of hospitalisations from a published study of RS virus epidemiology in Spain[91]. This produces estimates of the risk in the overall population;	Published data from Denmark is available; however, some of the publications are relatively old (2010-2015)[5] and using more up to date data was prioritised. A study by Nygaard et al. estimated hospitalisations rates between 2016-2020 and for the 2021/2022 season; however, the estimates for 2016-2020 are substantially lower than those of both the older published studies and the observed numbers in recent years [116].Using the data from the 2021/22 to 2023/24 season leads to approximately 1,600 hospitalisations in the standard of care scenario in the

	to obtain the risk in each risk-group, the distribution of risk between groups was obtained from published studies conducted in the US setting[92-94].	model, which fits well with the observed number of hospitalisations in Denmark. Additionally, the hospitalisation risk for all infants in the 2021/22 to 2023/24 seasons was 2.88%, which is very similar to the 2.94% reported by Jepsen et al[5]. The distribution by risk group and age by month does not change the overall risk of hospitalisation, but only impacts in which infants and at what age hospitalisations occur. Although the US health care system is markedly different from the Danish, the distribution of risk by subgroup is assumed to be similar. The estimated risks by month of age and risk group have been clinically validated. The model has functionality to choose to base the estimates of RSV hospitalisations on data published by Nygaard et al.
Risk of intensive care and mechanical ventilation conditional on RSV hospitalisation	The proportion of hospitalised infants receiving intensive care have been obtained from registry data on Danish infants (<1 year of age) hospitalised with RSV infection between 2010 and 2022.[88]The registry study only provided information on the overall population, so the distribution between subpopulations has been done using distributions observed in a published study conducted in the US setting [95] In the base-case, the risk of mechanical ventilation is taken from a study by Nygaard et al., which estimates rates of mechanical ventilation per hospitalisation. The model contains the functionality to choose rates obtained from the same registry study as the risk of intensive care[116].	Intensive care was identified by using the procedure codes *NABE (intensiv observation)* and *NABB (intensiv behandling)* which were associated with the same contact-number as an RSV hospitalisation. In the registry study, mechanical ventilation was identified by using the procedure code *BDGA (respirator behandling og anden assisteret ventilation)*, excluding *BGDA6*-codes which are related to manual ventilation. The estimated risks by month of age and risk group have been clinically validated.
Risk of pediatric emergency admission visit	For the risk of pediatric emergency department visits no reliable estimates for Denmark have been obtained, therefore the estimated rates are based on a published study	The estimated risks by month of age have been clinically validated.

	conducted in the United States[117].[117]. The study did not report data stratified by risk group, so only the rate for the overall population is included in the model.	
Risk of primary care visits	For primary care visits, a recently published study, based on a UK analysis, estimated five primary care visits per one RSV-coded hospitalisation in children aged 0-5 months and 12.5 primary care visits per one RSV-coded hospitalisation in children aged 6-11 months[118].[118]. These estimates were applied to the hospitalisation rate in the overall population, as no information about the distribution of risk between risk groups is available.	The estimated risk by month of age has been clinically validated.
Proportion of hospitalisations with subsequent "open admission"	Not included as an additional cost	Based on clinician feedback, a substantial number of infants hospitalised with RSV get an "open admission" on discharge; however, it is likely that this is already included in the DRG tariff for hospitalisations, therefore, additional costs for open admissions following hospitalisation are not applied.
Proportion of pediatric emergency department visits with subsequent "open admission"	80%	Based on clinician feedback, almost all infants seen with RSV in the pediatric emergency department will get an "open admission".
Risk of recurrent wheezing as a complication of MA RSV infection	First year: 31% Second year: 27% Third year: 17%	A German study found that 31% of infants hospitalised with RSV under 1 year of age developed wheezing.[46] A retrospective cohort study from 2013 found that for children with uncomplicated hospitalisations associated with RSV in infancy, 27% of children had wheezing after two years, falling to 17% after three years.[119] While the specific risk of recurrent wheezing following RSV hospitalisation is difficult to quantify, a systematic review of studies examining the association between RSV and wheezing found that at <36 months follow-up, the OR for recurrent

		wheezing for infants infected with RSV versus infants with no respiratory symptoms was 3.05 (95% CI: 2.50 to 3.71)[120]
RSV mortality	The risk of RSV mortality is based on a risk of mortality conditional on hospitalisation on 0.04%	A Danish study found that the case fatality rate for Danish children hospitalised with RSV was 0.04%[5]. This number is for children <5 years of age, but as risk of death is expected to be higher at lower ages, the estimate is conservative.

Abbreviations: NMA= Network meta analysis, MA= medically attended, RSV= respyratory syncytial virus

Mortality

The model included all-cause mortality, which was applied to remove infants who die due to any cause. The all-cause mortality rates are stratified by age so that a different mortality rate can be applied to infants aged 0 to 5 months, 6 to 11 months, and 12 to 59 months. In the model, the base case analysis included all-cause mortality rates that are stratified both by subpopulation and age (informed by CDC National Vital Statistics[121]).[121]). Separately, for the Danish setting, the all-cause mortality rates are informed by the DMC reference document: "Key figures including general mortality within the Danish population" which only stratifies by age. Users can switch between US or Danish data for transparency. For detailed information refer to the table below.

Table 28 All-cause mortality

	0-5 months	6-11 months	12-59 months	Use in the CEM
Danish general population mortality	0.003*	0.003*	0.00011*[a]	Not in the base case (optional for the user)
CDC National Vital Statistics	0.0059	0.0059	0.0059	Yes, in the base case

* Weighted 1-year probability by gender informed by DMC "Key figures including gnereal mortality within the Danish population"

Note: [a] Average of age 1 to 4 years (12 months to 59 months)

In addition to all-cause mortality, users can choose to include additional disease-related mortality which can be accounted for following three different approaches:

- Mortality based on a risk of mortality conditional on hospitalisation (0.04%)[5]
- Mortality based on a case (MA-RSV LRTI – in any health setting)
- Overall RSV mortality rate

However, as outlined in Table 53 and Table 54, in the base case analysis, the mortality is based on a risk of mortality conditional on hospitalisation (0.04%)

8.5 Overview of modelled average treatment length and time in model health state

NA

Table 29 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
NA	NA	NA	NA

Abbreviations: NA= not applicable or not available

NA

Table 30 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
NA	NA	NA	NA

Abbreviations: NA= not applicable or not available

9. Safety

9.1 Safety data from the clinical documentation

Safety data from the studies included in the NMA is presented in Table 31. No serious adverse events occurred in more than 5% of participants. Safety data from MEDLEY (in palivizumab eligible infants) is provided in Appendix K. Due to the difference in time-points between nirsevimab and Abrysvo trials (see notes to Table 31) network meta-analysis of safety outcomes was not considered appropriate.

Table 31 Overview of safety events in studies included in the NMA.

	MELODY NCT03979313 [a]		Griffin et al. 2020 NCT02878330 [b]		HARMONIE		Simoes et al. 2022[d]		MATISSE	
	Nirsevimab (n=1997)	Placebo (n=997)	Nirsevimab (n=968)	Placebo (n=479)	Nirsevimab (n=4015)	No intervention (n=4020)	Abrysvo (n=325)	Placebo (n=78)	Abrysvo (n=3568)	Placebo (n=3558)
Number of adverse events, n	8564	4167	3560	1842	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Number and proportion of patients with ≥1 adverse events, n (%)	1722 (86.2%)	843 (84.6%)	834 (86.2%)	416 (86.8%)	[redacted]	[redacted]	140 (43.1%)	30 (38.5%)	1324 (37.1%)	1228 (34.5%)
Number of serious adverse events*, n	194	94	150	132	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported

	MELODY NCT03979313 [a]		Griffin et al. 2020 NCT02878330 [b]		HARMONIE		Simoes et al. 2022[d]		MATISSE	
	Nirsevimab (n=1997)	Placebo (n=997)	Nirsevimab (n=968)	Placebo (n=479)	Nirsevimab (n=4015)	No intervention (n=4020)	Abrysvo (n=325)	Placebo (n=78)	Abrysvo (n=3568)	Placebo (n=3558)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	149 (7.46%)	83 (9.7%)	108 (11.16%)	81 (16.91%)	[redacted]	[redacted]	69 (21.2%)	12 (15.4%)	553 (15.5%)	542 (15.2%)
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	Not available	Not available	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	79 (4.0%)	41 (4.1%)	77 (8.0%)	60 (12.5%)	[redacted]	[redacted]	13 (4%)	3 (3.8%)	Not reported	Not reported
Number of adverse reactions (Treatment-related), n	26	19	Not available	Not available	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Number and proportion of	25 (1.3%)	15 (1.5%)	22 (2.3%)	10 (2.1%)	[redacted]	[redacted]	0 (0%)	0 (0%)	Not reported	Not reported

	MELODY NCT03979313 [a]		Griffin et al. 2020 NCT02878330 [b]		HARMONIE		Simoes et al. 2022[d]		MATISSE	
	Nirsevimab (n=1997)	Placebo (n=997)	Nirsevimab (n=968)	Placebo (n=479)	Nirsevimab (n=4015)	No intervention (n=4020)	Abrysvo (n=325)	Placebo (n=78)	Abrysvo (n=3568)	Placebo (n=3558)
patients with ≥ 1 adverse reactions, n (%)										
Number and proportion of patients who had a dose reduction, n (%)									N/A	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)									N/A	
Number and proportion of patients who discontinue treatment due to adverse events, n (%)									N/A	

[a] MELODY: Population: As-treated population; Time-point: 360 days post dose. Source: clinical study report[122] and clinicaltrials.gov
[b] Griffin et al. 2020: Population: As-treated population; Time-point: 360 days post dose ; Source: clinical study report[123] and clinicaltrials.gov
[c] HARMONIE: [redacted]
[d] Simoes et al. 2022: Population: Time-point: 1 month after birth ; Source: Simoes et al. 2022[109]
[e] MATISSE: Population: All infants born to vaccinated mothers; Time-point: Non-serious AEs = 1 month after birth, serious AEs = to 24 months of age; Source: Kampmann et al. 2023[79a] MELODY: Population: As-treated population; Time-point: 360 days post dose. Source: clinical study report[122] and clinicaltrials.gov
[b] Griffin et al. 2020: Population: As-treated population; Time-point: 360 days post dose ; Source: clinical study report[123] and clinicaltrials.gov
[c] HARMONIE: [redacted]; Source: clinical study report[124]
[d] Simoes et al. 2022: Population: Time-point: 1 month after birth ; Source: Simoes et al. 2022[109]
[e] MATISSE: Population: All infants born to vaccinated mothers; Time-point: Non-serious AEs = 1 month after birth, serious AEs = to 24 months of age; Source: Kampmann et al. 2023[79]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Abbreviations: NA= not available, CTCAE= Common Terminology Criteria for Adverse Events

Table 32 Serious adverse events

Adverse events	Intervention (N=x)	Comparator (N=x)
NA		

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Abbreviations: NA= not available

Due to the very safe nature of nirsevimab and Abrysvo, with no serious adverse events occurring in more than 5% in any of the trials, no adverse events are included in the health economic model.

Table 33 Adverse events used in the health economic model

Adverse events	Intervention	Comparator
N/A		

Abbreviations: NA= not available

9.2 Safety data from external literature applied in the health economic model

Table 34 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)	Comparator (N=x)	Difference, % (95 % CI)
N/A			

Abbreviations: NA= not available

10. Documentation of health-related quality of life (HRQoL)

There is an overall scarcity of RSV-associated health-related quality of life data for both infants and caregivers. The QALY-relevant inputs for the cost-effectiveness model were selected based on estimates available in the literature at the time the cost-effectiveness analysis was conducted.

Section 10.1 is not relevant for this submission as external utility decrements have been selected.

Section 10.2 Presents the alternative options for utility decrements and the ones selected in the base case.

Section 10.3 Presents the studies from which the utility decrements have been selected.

Table 35 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
NA	NA	NA

Abbreviations: NA= not available

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

NA

10.1.2 Data collection

NA

Table 36 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
NA				

Abbreviations: NA= not available

10.1.3 HRQoL results

NA

Table 37 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: NA= not available

10.2 Health state utility values (HSUVs) used in the health economic model

The impact of RSV related health events and long-term complications from an RSV infection on infants' quality of life and the impact of an infant RSV case on parents/caregivers are captured in the model as a decrement in overall QALYs. A QALY decrement is associated with each health event related to an RSV case and complications experienced in the inpatient and outpatient setting. Depending on the strategy being assessed, different proportions of infants will experience adverse events, generating incremental QALYs that will inform the base-case ICER.

10.2.1 HSUV calculation

No HSVU calculation has been performed since the analysis relied on relative utility decrements, based on RSV-related adverse events applied to a baseline value. The decrements are applied as a one-time QALY loss per RSV-related adverse event and are not differentiated by subpopulation in age in months. A publication from RESCEU provided

an updated estimate of QALY losses due to RSV in infants aged <1 year, with additional estimates stratified by HCRU.[125]

10.2.1.1 Mapping

Due to data scarcity, no mapping has been performed in the analysis.

10.2.2 Disutility calculation

Based on the results of the HRQoL pragmatic literature review (Appendix I), we selected the study from Mao et al. to inform disutility parameters associated with RSV events. Decrements are applied as a one-time QALY loss per RSV-related event and are not differentiated by subpopulation nor the age of the infant. The impact of an infant RSV episode on parents/caregivers' utility are included in a sensitivity analysis. The QALY loss per RSV-related event used in the model base-case are derived from Mao et al 2022[95] and include:

- Hospitalizations
- ICU
- MV
- Pediatric department visit
- Primary care visit
- Open hospitalisation

Annual QALY loss associated with longer complications, not strictly related to RSV infections (i.e. wheezing), was informed with targeted studies identified outside the SLR, as restricting the search to RSV, limited the type of information available. Specifically the annual QALY loss of wheezing was derived from Li et al 2022[87], which in their study re-elaborated data from Willems et al.[126] on asthmatic children and adults. [126] on asthmatic children and adults. Longer complications included in the model where:

- Recurrent wheezing

Two main studies have been showing utility decrements for children hospitalization for RSV or severe RSV; Mao et al and Hodgson et al[86,127].[86,127]. The annual quality life loss (QALY) for one RSV episode under the age of one year is larger from Mao's study (0.0063) compared to Hodgson's study under the age of five years (0.0038) [86,127]. There are some differences between these two studies: [86,127]. There are some differences between these two studies:

- The QALY loss estimate by Hodgson et al for RSV among children under the age of five was from a survey after the confirmed RSV case, while Mao et al assessed health status during confirmed RSV in children under one year old.
- QALY loss in the Hodgson study was calculated based on a shorter symptom duration (median 5 days) than the reported symptom duration in Mao (mean 12.5 days). According to the Swedish Medical Products Agency, hospitalization is at day 4-5 of the course of illness and Swedish Registry data states that the average number of days hospitalized is 4 days, but if the infant needs ventilation supports the average is 9 days for MV, 7 days for CPAP and 5.6 days for high flow nasal cannula [3, 11]. Hence, the mean of 12.5 days captures a more accurate symptom duration for the Swedish setting.

- Hodgson used the full EQ-5D health profile, and the UK value set of EQ-5D-3L to calculate QALY for very young children but questions such as “mobility”, “looking after myself” and “usual activities” were less appropriate for use in valuing the health of an infant less than one year.
- Mao et al assumed the baseline HRQoL of infants to be in full health which can overestimate QALY loss.
- Because RSV disease severity is higher in infants under one year old and decreases with age[26], QALY loss is likely greater for children younger than one compared to those under five years. Diez-Gandia[128] calculated the HRQoL loss to be 37.5% and 31.5% on days 0 and 7 since the diagnosis of the disease, respectively, which was comparable to the results in Mao et al. Mao et al observed a mean HRQoL loss of 29% and 46% for ambulatory care and hospitalised infant patients on the worst day, respectively. The slight discrepancy may be due to the different questionnaires used and because Diez-Gandia and colleagues did not differentiate between caregivers and children for calculating HRQoL loss (they combined children’s symptoms, children’s behaviours, parents’ concerns, parents’ emotions and the impact of the infection on family activities.

The differences in the estimates from the two studies can be explained in part by differences in the study population, as the RESCEU study[125] assessed HRQoL in children aged <1 year with confirmed RSV, whereas the QALY loss estimate from the study by Hodgson et al. (2022)[129] (2022)[129] was approximated in children aged <5 years with RSV-like symptoms (not confirmed cases). For this reason and given that the duration of symptoms reported in Denmark aligns better with Mao et al, the model is informed using a decrement of 0.0063 per hospitalization.

10.2.3 Mortality-related disutility

If RSV-related mortality is included in the analysis, the model allows for the application of a lifetime QALY loss associated with premature death. These estimates represent the QALYs lost due to each RSV-related infant death. The lifetime QALY loss is calculated as the cumulative total utility per year starting from birth to the life expectancy. The EQ-5D population norms for the Danish population and the average life expectancy in Denmark (81.5 years[130]) were used to derive the total QALY loss. The EQ-5D population norms for the Danish population and the average life expectancy in Denmark (81.5 years[130]) were used to derive the total QALY loss. A discount rate is applied to the health outcomes as described in 4.1.1.

Table 39 presents the total QALY loss associated with each premature death applied in the base-case in the Danish setting.

10.2.4 HSUV results

Calculations for disutilities adapted from Mao et al, are reported in Appendix J.

Table 38 Overview of RSV related disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
QALY loss per event				
Hospitalizations (incl. ICU admission and MV)	0.0101	modified EQ-5D	Pooled*	Mao et al 2022
ICU: Conditional on Initial Hospitalization	0.0101	modified EQ-5D	Pooled*	Mao et al 2022
Mechanical ventilation: Conditional on Initial Hospitalization	0.0101	modified EQ-5D	Pooled*	Mao et al 2022
Pediatric department visit	0.0063	modified EQ-5D	Pooled*	Mao et al 2022
Primary care visits	0.0063	modified EQ-5D	Pooled*	Mao et al 2022
Annual QALY loss per complication				
Recurrent wheezing	0.0392	EQ5D-3L-Y	UK	Li et al 2022
Asthma	0.0381	EQ5D-3L-Y	UK	Li et al 2022

Abbreviations: QALY= Quality adjusted life years; CI= confidence intervals

Note: Utility scores pooled across Spain, UK, Finland, The Netherlands

Table 39 Total utility loss per premature death

	Value
Life expectancy (discounted)	27.78
Life expectancy (undiscounted)	81.5
Lifetime QALY loss (discounted)	23.31
Lifetime QALY loss (undiscounted)	60.27

Abbreviations: QALY= Quality adjusted life years

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

QALY decrements have been derived from the existing literature at the time of the submission. This section presents the studies used to inform the model.

10.3.1 Mao Z. et al. 2022

Study design

This prospective observational multi-country cohort study recruited healthy term-born infants in four European countries (UK, Spain, Finland and the Netherlands) between July 2017 and November 2019 which were actively followed until their first birthday during the RSV seasons of 2017/18, 2018/19 and 2019/20.

Infants were recruited at birth and a background questionnaire was completed at intake by caregivers (mother, father or other) to record infants' and caregivers' background characteristics (including socio-demographics and potential risk factors). During the RSV season in the first year of life, parents were contacted weekly and if the child had respiratory symptoms, a nasal sample was taken during a home visit and the sample was analysed for RSV.

Caregivers (one caregiver in each household) were asked to rate their and their children's HRQoL during the RSV episode based on the EQ-5D instrument. Each day, caregivers were asked to answer the ''Usual Activities" (UA) and ''Anxiety/Depression" (AD) dimensions from the EQ-5D-5L and the EQ-5D-VAS (visual analogue scale) for themselves, and to complete the ''Pain/Discomfort" and ''Sad" dimension from EQ-5D-3L-Y and the EQ-5D-VAS for their infants. Because not all dimensions of the EQ-5D were measured, instead of calculating health utility scores, the authors calculated the differences in disutility of the two available health dimensions between baseline and on each diary day and assumed the other three health dimensions did not change due to RSV infection. For example, if a caregiver had no problem [level 1] in UA and AD at baseline and reported level 3 problems in these two dimensions on diary Day 1, the utility loss on Day 1 would be: (1-UA3-AD3) - (1-UA1- AD1) = UA1-UA3 + AD1-AD3. UAn and ADn are the coefficients in EQ-5D's valuation regression models for calculating the utility values, representing the estimated disutility of having problems on dimension UA or AD at level n. In this study, the utility loss can be quantified as a quality-adjusted life day (QALD) loss.

Total QALD loss was obtained for each episode. Because no HRQoL was collected for infants at age one year and there are no population norms for infants of this age in most countries, baseline HRQoL was assumed to be in full health (no problem in Sad and Pain dimension). For infant QALD losses, the only published Western European EQ-5D-Y valuation model was used, which was for Spain.

Results

180 RSV episodes had full EQ-5D data, with 36 cases occurring in Spain, 14 in Finland, 69 in the UK, and 48 in the Netherlands.

QALD loss associated with RSV hospitalizations was 3.7 (3.3; 4.3). Which over a year translates into a utility decrement of 0.01014.

10.3.2 Li X. et al 2022

Study design

The study aimed at evaluating the health and economic burden of RSV infections and the cost-effectiveness of RSV disease prevention strategies, including both seasonal and year-round programs in Norwegian children under 5 years of age.

To inform their input parameters Li et al. relied on a UK study which used the EQ5D-3L-Y questionnaire in children under 5 years of age with RSV infections. However, QALY value of recurrent wheezing and asthma were based on a review on health utilities of four common diseases, including asthma in paediatric patients[131]. To inform their input parameters Li et al. relied on a UK study which used the EQ5D-3L-Y questionnaire in children under 5 years of age with RSV infections. However, QALY value of recurrent wheezing and asthma were based on a review on health utilities of four common diseases, including asthma in paediatric patients[131].

Results

Using such data, Li et al. fitted a gamma distribution to quantify the uncertainty around the average QALY loss due to wheezing, resulting in an estimated annual QALY loss of 0.0392 (95% CI: 0.0116-0.0632).

10.3.3 HRQoL Results

Results from these studies have been used to inform Table 38 of section 10.2.4

10.3.4 HSUV and disutility results

Results from these studies have been used to inform Table 38 of section 10.2.4

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Abbreviations: NA= not applicable or not available.

Table 41 Overview of literature-based health state utility value

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
QALY loss per event				
Hospitalizations (incl. ICU admission and MV)	0.0101	modified EQ-5D	Pooled*	Mao et al 2022
ICU: Conditional on Initial Hospitalization	0.0101	modified EQ-5D	Pooled*	Mao et al 2022

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Mechanical ventilation: Conditional on Initial Hospitalization	0.0101	modified EQ-5D	Pooled*	Mao et al 2022
Pediatric department visit	0.0063	modified EQ-5D	Pooled*	Mao et al 2022
Primary care visits	0.0063	modified EQ-5D	Pooled*	Mao et al 2022
Open hospitalisation "åben indlæggelse"	0.0038	modified EQ-5D	Pooled*	Mao et al 2022
Annual QALY loss per complication				
Recurrent wheezing	0.0392	EQ5D-3L-Y	UK	Li et al 2022
Asthma	0.0381	EQ5D-3L-Y	UK	Li et al 2022

Abbreviations: QALY= Quality adjusted life years, ICU= intensivi care unit, MV= mechanical ventilation

Note: Utility scores pooled across Spain, UK, Finland, The Netherlands

11. Resource use and associated costs

The models include direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines[132]. All costs are valued in 2024 Danish Krone (DKK) (except costs sourced from the DMC unit cost catalogue, 2023)[133]. The following section regarding cost and resource use is mainly presented per subpopulation (overall, palivizumab eligible infant population, preterm infant population, and term infant population), containing information regarding drug acquisition costs (cost of prophylaxis and potential AE costs), RSV event/treatment management costs, RSV specific complication costs, and patient time/transportation costs.The models include direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines[132]. All costs are valued in 2024 Danish Krone (DKK) (except costs sourced from the DMC unit cost catalogue, 2023)[133]. The following section regarding cost and resource use is mainly presented per subpopulation (overall, palivizumab eligible infant population, preterm infant population, and term infant population), containing information regarding drug acquisition costs (cost of prophylaxis and potential AE costs), RSV event/treatment management costs, RSV specific complication costs, and patient time/transportation costs.

Drug costs are sourced from Medicinpriser.dk [134] (Beyfortus® is not registered at Medicinpriser.dk, however, Sanofi is aiming for a net price agreement for Beyfortus®,) and applied as pharmacy purchasing prices (AIP). Drug costs are sourced from Medicinpriser.dk [134] (Beyfortus® is not registered at Medicinpriser.dk, however, Sanofi is aiming for a net price agreement for Beyfortus®,) and applied as pharmacy purchasing prices (AIP). Disease management and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024 and DMC catalogue for unit costs (2023)[133]. Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs.

11.1 Medicine costs - intervention and comparator

The cost per dose of prophylaxis includes the unit acquisition cost and the per-unit administration cost. The total prophylaxis costs are aggregated by the number of immunized infants and the number of doses each infant receives to determine the total cost of prophylaxis in each subpopulation. Dosing details for nirsevimab, palivizumab, and maternal immunisation can be found in Section 3.4.1, 3.5.1, and 3.5.2 respectively (see also Table 42 for summary of dosing details).

Nirsevimab Beyfortus®

Dosing specified in Section 3.4.1. In the model, the price for nirsevimab is a weighted average of the list price for nirsevimab (based on the assumption that 60% of infants weigh above 5kg). Please note that Sanofi are aiming for a net price agreement for nirsevimab. The AIP cost of nirsevimab is provided in Table 43.

Palivizumab

Dosing specified in Section 3.5.1. Palivizumab (15 mg/kg) is given intramuscularly with a month's interval, rounding up doses to avoid wastage. The cost per infant is calculated based on weight from a Swedish study on palivizumab with 5 injections per infant. The first dose should be given before the start of the RSV season, planned around mid-November but may be modified depending on the RSV season. Therefore, the total prophylaxis cost is equal to the average cost per the included RSV season. The cost of palivizumab is calculated per mg and does not include waste (conservative). The AIP cost of palivizumab is given in Table 43. A conservative approach has been taken, using the average of the two available packages of palivizumab.

Maternal immunisation

Dosing specified in Section 3.5.2. Pregnant women can be vaccinated between 24+0 and 36+0 weeks of gestation. Infants born to vaccinated mothers are immunised from RSV up to 6 months. The AIP cost of maternal immunisation is given in Table 43.

Table 42 Prophylaxis dosing and frequency used in the model

Medicine	Groups	Dose	Relative dose intensity	Frequency	Vial sharing
Nirsevimab (Beyfortus®)	<5 kg	50 mg	NA	Single dose	No
	≥ 5kg	100 mg			

Medicine	Groups	Dose	Relative dose intensity	Frequency	Vial sharing
Palivizumab (Synagis®)	Palivizumab is available in 50mg and 100mg packages; doses are weight dependent but are rounded up to eliminate wastage[2].	15 mg / kg	NA	Once a month during RSV period	No
Maternal immunisation (Abrysvo®)	Between weeks 24 and 36 GA	0.5 mL	NA	Single dose	No

Abbreviations: NA= Not applicable or not available, GA= Gestational age, RSV= respiratory syncytial virus

Table 43 Prophylaxis costs used in the model

Administration type	Frequency	Strength	Package size	Pharmacy purchase price (DKK)
Nirsevimab (Beyfortus®)	Single dose	[redacted]	[redacted]	[redacted]
Palivizumab (Synagis®)	Once monthly during the RSV season	[redacted]	[redacted]	[redacted]
Maternal immunisation (Abrysvo®)	Single dose	[redacted]	[redacted]	[redacted]

Abbreviations: RSV= Respiratory syncytial virus

11.2 Medicine costs – co-administration

The model also separately aggregates the costs associated with additional PC visits based on physician monitoring or visit at an outpatient clinic (in hospital) of the response and reaction to the prophylaxis measure following immunization or to include costs for treatment for children born out of the season. These costs are based on the unit cost per visit and the number of additional PC visits associated with each prophylaxis measure. The base case assumes that infants require an additional PC (referred to as "GP" visit in the cost-effectiveness model(s)) visits following the administration of prophylaxis with palivizumab, nirsevimab, or maternal immunisation. As the setup for administration of the included interventions is currently unknown, similar costs have been assumed for all treatment modalities.

Table 44 additional visits related to intervention and comparators

Resource	Frequency	Unit cost [DKK]	DRG code	Reference
Physician care visit	1 additional visit	153,50	None	DMC unit cost catalogue 2023

11.3 Administration costs

In the base case, the cost of administration is set to 0 DKK as it has been assumed that nirsevimab, palivizumab, and maternal immunisation will be administered during scheduled and standard visits. Furthermore, it is assumed that any administration cost will be similar between the comparators.

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Nirsevimab administration	Single administration	0 DKK	NA	NA
Palivizumab	Once monthly during the RSV season	0 DKK	NA	NA
Maternal immunisation	Single administration	0 DKK	NA	NA

Abbreviations: NA= Not applicable or not available, DRG= diagnosis-related groups, RSV= respiratory syncytial virus

11.4 Disease management costs (RSV specific events)

The treatment costs for RSV are stratified by subpopulation and calculated by and aggregated cost per stay.

The model calculates cases of hospitalization with intensive care and observation and mechanical ventilation due to RSV MA-LRTI as a proportion of infants hospitalized for RSV MA-LRTI. It then assigns the costs associated with intensive care and observation, MV, and inpatient hospitalizations based on these groups. Therefore, the cost of intensive care and observation includes the cost of inpatient hospitalization plus intensive care and observation (excluding MV), and the cost of MV includes the cost of inpatient hospitalization, intensive care and observation with MV.

Table 50 below gives the overview of the base case health event settings corresponding to included treatment costs.

Table 46 Health event settings in the models

Activity	Included
Hospitalizations Alone	Yes
Intensive care and observation (incl. hospitalization)	Yes
Mechanical ventilation (incl. hospitalization and intensive care and observation)	Yes

Activity	Included
Pediatric department visit	Yes
Primary care visits	Yes
Open hospitalisation "åben indlæggelse"	Yes
All-cause LRTI hospitalizations (excl. RSV)	No

Abbreviation: RSV= respiratory syncytial virus, LRTI= lower respiratory tract infection

Treatment costs included in the model are hence provided in Table 47. In line with Danish clinical insights, it's observed that in roughly 80% of infant hospital admissions the practice of "open hospitalisation" / admission ("åben indlæggelse") is common. However, in the base case, a cost per bed day applies exclusively to outpatient hospitalizations or visits (pediatric emergency admission visits), set at 3,321 DKK per day (as outlined in the table below). It is assumed that inpatient hospitalizations already include "open hospitalisation" within their tariffs, encompassing a longer "trim point." However, the model allows for changing the proportion of patients in outpatient to 50% as well (scenario). In the absence of the duration of "open hospitalisation" for pediatric emergency admission visits visit, the base case applies one bed day. This can be changed in the model. However, scenario analysis employs 3 bed days. The frequency of each health resource use is based on Danish registry or surveillance data for each event (described in Section 8.4).

Table 47 RSV management costs used in the models

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Hospitalizations Alone	Frequency is calculated based on RSV event risk, see Table 105 in Appendix L	See Table 48	See Table 48	DRG 2024
Intensive care and observation (incl. hospitalization)	Frequency is calculated based on RSV event risk, see Table 106 in Appendix L	See Table 48	See Table 48	DRG 2024
Mechanical ventilation (incl. hospitalization and intensive care and observation)	Frequency is calculated based on RSV event risk, see Table 107 in Appendix L	See Table 48	See Table 48	DRG 2024
Pediatric department visit	Frequency is calculated based on RSV event risk, see Table 108in Appendix L	3,321.00	15MP15	DRG 2024
Primary care visits	Frequency is calculated based on RSV event risk, see Table 109 in Appendix L	153.61	NA	DMC unit cost catalogue
Open hospitalisation "åben indlæggelse"	Associated and linked with outpatient admissions (80% of all outpatient admissions in the base case)	3,321.00	15MP15	DRG 2024

Abbreviations: NA= Not applicable or not available, DMC= Danish Medicines Council, DRG= diagnosis-related groups, RSV= respiratory syncytial virus

From the Danish DRG tariff database, inpatient hospitalisations, intensive care and observation (NABE), and MV (BDGA group) can be grouped to the action diagnosis

"DB974". Different DRG tariff can be found based on the level of complication/severity, which is again based on GA. Based on Danish clinical feedback, CPAP is used in 75% of the cases in infants < 6months and in 50% in infants > 6months, when hospitalised. This is accounted for in the DRG tariff, since CPAP is included using the procedure code BGFC32, both for hospitalisation tariffs >12 hours or <12 hours. Refer to Table 48.

Regarding the translation from GA in weeks to fit the modelled subpopulations palivizumab eligible infants, preterm infants, and term infants, the week stratifications for the modelled populations have been used as guidance, although the week stratification from the DRG tariffs does not completely fit with the subpopulations defined in the model (see Section 4.1.1 for modelled subpopulations), resulting in:

- GA <28 weeks = palivizumab eligible infants (infants born before 29 weeks GA)
- GA 28-31 weeks and 32-35 weeks = preterm infants (infants born between 29 GA and 34 weeks and six days of gestational age)
- GA >35 weeks = term infants (infants born at or after 35 weeks GA)

Table 48 Inpatient hospitalisations, ICU (incl. hospitalisation), and MV by GA

Activity	GA (<28 weeks)	GA (28-31 weeks)	GA (32-35 weeks)	GA (>36 weeks)	Comment and reference
Hospitalizations Alone	219,171.00 15MP05	180,478.00 15MP08	71,858.00 15MP11	20,868.00 15MP14	DRG 2024
Intensive care and observation (incl. hospitalization)	245,958.00 15MP04	209,111.00 15MP07	111,198.00 15MP10	54,129.00 15MP13	Procedure code: NABE
Mechanical ventilation (incl. hospitalization and intensive care and observation)	435,033.00 15MP03	336,117.00 15MP06	191,139.00 15MP09	180,448.00 15MP12	Procedure code: BDGA and BGFC32

Abbrevations: GA= gestational age, DRG= diagnosis-related groups

11.5 Costs associated with management of RSV specific complications

The cost associated with complications is applied as a single, one-off management cost by subpopulation evenly across all complications. Table 50 below gives the overview of the RSV specific complications settings applied in the base case.

Table 49 Complications settings in the models

Complication	Included
Recurrent wheezing	Yes
Asthma	No
Excess HCRU	No
Otitis media	No
Recurrent wheezing year 2	Yes
Recurrent wheezing year 3	Yes

Abbreviation: HCRU= health care resource use

Due to the lack of data on asthma, excess HCRU, and otitis media, only wheezing is considered for the base case analysis.

Recurrent wheezing

As recurrent wheezing is the only long-term complication included in the analysis, the cost of managing recurrent wheezing is assumed to be equal to that of 5.5 PC visits plus one beta agonist inhaler[26]. As applied to the risk of recurrent wheezing, the cost associated with recurrent wheezing that occurs in year 2 or 3 of an infant's life is discounted based on an annual discounting rate of 3.5%. The costs associated with recurrent wheezing are presented in Table 50 below.

Table 50 Cost associated with management of RSV complications

	Unit cost/DRG tariff	DRG code / other	Assumptions
Recurrent wheezing	153.50 DKK per visit	DMC unit cost catalogue	5.5 PC visits + one beta agonist
Recurrent wheezing year 2	153.50 DKK per visit	DMC unit cost catalogue	5.5 PC visits + one beta agonist
Recurrent wheezing year 3	153.50 DKK per visit	DMC unit cost catalogue	5.5 PC visits + one beta agonist
Beta agonist inhaler	49.29 DKK	Medicinpriser.dk	Airomir (salbutamol) at Medicinpriser.dk (nr: 376434)

Abbreviations: DRG= diagnosis-related groups, NA= Not applicable or not available, PC= primary care visit, DMC= Danish Medicines Council

11.6 Subsequent treatment costs

Not applicable.

11.7 Patient costs

Patient costs for transportation and time have been included based on the requirements from the DMC. A conservative approach has been undertaken and the estimation of patient time and transportation related costs are based on the frequency of healthcare resources described in sections described above (RSV treatment, complication management etc). Based on DMC's unit cost catalogue (2023), a unit cost of 140 DKK was applied to all visits and healthcare activities in the model to account for travel expenses, and a unit cost of 203 DDK was used for all patient hours spent on treatment-related activities. The model includes patient hours spent on treatment-related activities regarding:

- Prophylaxis treatment (including potential AE for nirsevimab e.g.). Note that administration costs are not included in the model as it is assumed that the administration costs would be similar for nirsevimab vs SoC and nirsevimab vs maternal immunisation.
- Management of RSV events (disease management)
- Management of RSV specific complications

The estimation of the time spent for each event or complications is based on the following items:

- Inpatient admissions include hospitalisation alone, intensive care and observation (incl. hospitalization) and mechanical ventilation (incl. hospitalization and intensive care and observation)
- Outpatient admissions / visits include paediatric department visit and open admission.
- PC visits
- Add. Physician visit after nirsevimab administration
- 5.5 PC visits for complication management

A very conservative approach has been taken, using the DRG tariff trim point for inpatient admissions to estimate the number of days/hours spent by patient (or parent). The cost-effectiveness model has a placeholder for clinical expert input as well. However, Sanofi has no clinical expert input to add.

Transportation costs are included for all admissions or visits and are as mentioned sourced from DMC's unit cost catalogue (140 DKK per visit). Refer to Table 51 and Table 52 for an overview of applied assumptions regarding the estimation of patient time and transportations costs and the total cost per visit or one-off, respectively.

Table 51 Patient time assumptions, per visit

Activity	Time spent [minutes, hours, days]	Time spent [minutes, hours, days]	Time spent [minutes, hours, days]	Assumptions
	PVB	Pre	Term	
Patient time costs for RSV events				
Inpatient admissions	98 days (trim point)	35 days (trim point)	14 days (trim point)	Based on the DRG tariff data base, a conservative approach has been taken, using the trim point (days) as patient hours spent (unfortunately, InteraktivDRG does not inform anything about length of stay). In the base case, 12 patient hours is applied in model. However, this can be changed to 24 hours.
Outpatient admissions	12 hours	12 hours	12 hours	Assuming a "short stay" coded in Interaktiv DRG 2024. Below 12 hours.
PC visit	1 hour per visit	1 hour per visit	1 hour per visit	Assumption
Add. Physician visit after nirsevimab administration	0.5 hour	0.5 hour	0.5 hour	Assumption

Activity	Time spent [minutes, hours, days]	Time spent [minutes, hours, days]	Time spent [minutes, hours, days]	Assumptions
	PVB	Pre	Term	
Patient time costs for RSV complications				
PC visit	1 hour per visit	1 hour per visit	1 hour per visit	Assumption. 5.5 visits.

Abbreviations: PVB= Palivizumab eligible, Pre= preterm infants, Term= term infants, PC= primary care visit, DRG= diagnosis-related groups, RSV= respiratory syncytial virus

Table 52 Patient costs used in the model, per visit

Activity	Grouping	Total cost (DKK)	Total cost (DKK)	Total cost (DKK)
		PVB	Pre	Term
Patient time costs				
RSV treatment (management of events)	Inpatient RSV events	273,644.00	146,160.00	34,916.00
	Outpatient RSV events	2,436	2,436	2,436
	PC visits	203	203	203
	Add. Physician visit after nirsevimab administration (30 minutes)	101.50	101.50	101.50
RSV complications	One-off cost	558.25	558.25	558.25
Transportation costs				
RSV treatment (management of events)	140 DKK per visit	140	140	140
RSV complications	One-off cost (5.5 visits)	770	770	770

Abbreviations: PVB= Palivizumab eligible, Pre= preterm infants, Term= term infants, PC= primary care visit, RSV= respiratory syncytial virus

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model(s) 1 and 2 are presented in Table 53 and Table 54, respectively.

Table 53 Base case overview – Model 1 (maternal immunisation)

Feature	Description
Comparators	Maternal immunisation (Abrysvo®)
Strategy	Nirsevimab: Universal strategy for all groups. Maternal immunisation: Universal strategy for preterm and term infants.
Type of model	Decision tree
Time horizon	1 season
Measurement and valuation of health effects	Given that this assessment concerns infants for one RSV season. HRQoL has been addressed in terms of QALY decrements for RSV-associated hospitalisations and complications. Decrements have been taken from the literature and are presented further discussed in section 0. The impact of an infant RSV episode on parents/caregivers' utility are included in a sensitivity analysis.
Costs included	Prophylaxis costs Health care resource utilisation costs for RSV specific events, including a proportion of 80% in pediatric emergency admission visits that requires open admission - assuming 1 bed day. RSV specific complication costs Patient and transportation costs Refer to Table 46 and Table 49
Dosage of medicine	Nirsevimab: Based on weight, single dose Maternal immunisation: single dose of 0.5 ml
Timing of maternal immunisation	[redacted]
Period of intervention	November – for 4 months (based on visual inspection of infection rates, indicated by Figure 14).
Prevention efficacy	Nirsevimab: Palivizumab eligible infant population: 56% (non-inferiority) VE for both outpatient and inpatient setting Preterm infants: 79.16% VE (MA results see 7.1.3) for both outpatient and inpatient setting Term infants: 80.36% VE (NMA results see 7.1.3) for both outpatient and inpatient setting Maternal immunisation: 56.6% VE across groups for both outpatient and inpatient (NMA results see 7.1.3)

Feature	Description
Duration of protection	Nirsevimab: 5 months Maternal immunisation: 6 months
Treatment waning	Not included
Coverage rate	Nirsevimab: 80% across all groups (Refer to Table 27) Maternal immunisation: 0%, 21.5%, and 70% for the palivizumab eligible, preterm, and term group, respectively. (70% in the season 2023/24[48], refer to Table 27)
Disease related mortality	Risk based on inpatient hospitalisations

Abbreviations: RSV, Respiratory syncytial virus, HRQoL, health-related quality of life QALY, quality-adjusted life year; NMA, network meta-analysis, VE= vaccine efficacy

Table 54 Base case overview – Model 2 (SoC)

Feature	Description
Comparators	SoC (BsC and palivizumab (Synagis®))
Strategy	Nirsevimab: Universal strategy for all groups. SoC: Universal strategy for palivizumab eligible infants
Type of model	Decision tree
Time horizon	1 season
Measurement and valuation of health effects	Given that this assessment concerns infants for one RSV season. HRQoL has been addressed in terms of QALY decrements for RSV-associated hospitalisations and complications. Decrements have been taken from the literature and are presented further discussed in section 0. (...) The impact of an infant RSV episode on parents/caregivers' utility are included in a sensitivity analysis.
Costs included	Prophylaxis costs Health care resource utilisation costs for RSV specific events, including a proportion of 80% in pediatric emergency admission visits that requires open admission - assuming 1 bed day. RSV specific complication costs Patient and transportation costs Refer to Table 46 and Table 49
Dosage of medicine	Nirsevimab: Based on weight, single dose Palivizumab: 15 mg / kg once a month during RSV period
Timing of palivizumab	Administered to palivizumab-eligible infants per recommendations from the Danish Pediatric Society (i.e., once monthly during the RSV season)
Period of intervention	November – for 4 months (based on visual inspection of infection rates, indicated by Figure 14).
Prevention efficacy	Nirsevimab:

Feature	Description
	Palivizumab eligible infant population: 56% (non-inferiority) VE for both outpatient and inpatient setting Preterm infants: 79.16% VE (NMA results see 7.1.3) for both outpatient and inpatient setting Term infants: 80.36% VE (NMA results see 7.1.3) for both outpatient and inpatient setting SoC: 56% for the palivizumab eligible infant population (both outpatient and inpatient)
Duration of protection	Nirsevimab: 5 months SoC: 1 month
Treatment waning	Not included.
Coverage rate	Nirsevimab: 80% across all groups (Refer to Table 27) SoC: 75% for the palivizumab eligible group.
Disease related mortality	Risk based on inpatient hospitalisations

Abbreviations: BsC= best supportive care, RSV= respiratory syncytial virus, HRQoL= health-related quality of life, QALY= quality adjusted life year, GA= gestational age, NMA= network-meta analysis, VE= Vaccine efficacy

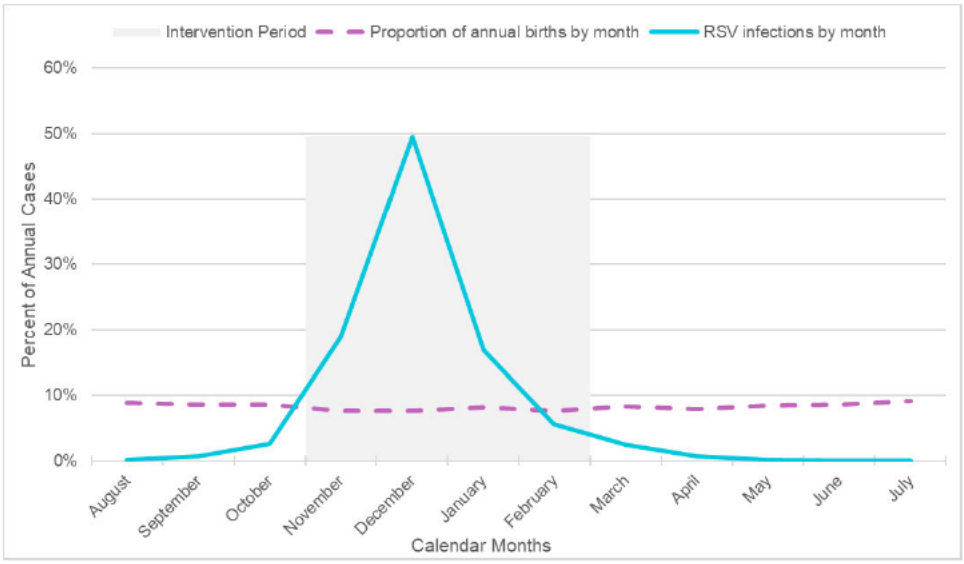


Figure 14 Period of intervention

12.1.1 Base case results

In the model base case where nirsevimab is compared against maternal immunisation (model 1) or against SoC (model 2) are presented in Table 55. Both models were utilising a time horizon of one season only. The results presented below covers the overall population and are not reported by subgroup. However, the subgroup "Term infants" accounts for 97% of infants based on Danish data.

Table 55 Base case results, discounted estimates

	Nirsevimab	SoC	Maternal immunisation with Abrysvo	Difference (nirsevimab versus SoC)	Difference (nirsevimab versus Abrysvo)
Medicine costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	NA	NA	NA	NA	NA
Administration	NA	NA	NA	NA	NA
Disease management costs (RSV treatment)	See below	See below	See below	See below	See below
Hospitalizations Alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICU: Conditional on Initial Hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mechanical ventilation: Conditional on Initial Hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paediatric department visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary care visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Open hospitalisation "åben indlæggelse"	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events (RSV complications)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	NA	NA	NA	NA	NA
Patient costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palliative care costs	NA	NA	NA	NA	NA
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Nirsevimab	SoC	Maternal immunisation with Abrysvo	Difference (nirsevimab versus SoC)	Difference (nirsevimab versus Abrysvo)
Life years gained (health state A)	NA	NA	NA	NA	NA
Life years gained (health state B)	NA	NA	NA	NA	NA
Total life years	**NA**	**NA**	**NA**	**NA**	**NA**
QALY loss associated with health events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY loss associated with complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY loss associated with premature death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALY loss	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes, other	See below	See below	See below	See below6	See below
Total number of hospitalisations (incl. ICU and MV)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of paediatric departments visit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Versus standard of care	Versus maternal immunisation with Abrysvo
Incremental costs per life year gained	[redacted]	[redacted]
Incremental cost per QALY gained (ICER)	[redacted]	[redacted]
Incremental cost per QALY saved (ICER)	[redacted]	[redacted]
Incremental cost per hospitalisation saved	[redacted]	[redacted]

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested. For the input parameters varied within the DSA, a ±20% variation from the base-case parameter value was assumed to determine the lower-bound and upper-bound values (Model sheet "DSA Inputs").

The variance of distribution of RSV infection by month is based on Danish registry data and may therefore be seen as best possible data available. Due to the conservative assumption to only model a 5-month effect of nirsevimab with no waning effect from month 6 onwards, although evidence supports the opposite, the true variance of this parameter may have less impact on the result. The DSA also show the importance of implementing the immunization strategy with nirsevimab at the seasonal outbreak, due to the conservative assumption of only 5 months effect of nirsevimab.

The 10 most influential model parameters (on the ICER results) from model 1 with nirsevimab vs maternal immunisation are presented in Table 56 and as a tornado diagram in Figure 15.

Table 56 One-way sensitivity analyses results – Model 1 (maternal immunisation)

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA= Not applicable or not available, ICER= incremental cost-effectiveness ratio, QALY= quality adjusted life year, RSV= Respiratory syncytial virus

The 10 most influential model parameters (on the ICER results) from model 2 with nirsevimab vs SoC are presented in Table 57 as a tornado diagram in Figure 16.

Table 57 One-way sensitivity analyses results – Model 2 (SoC)

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA= Not applicable or not available, ICER= incremental cost-effectiveness ratio, QALY= quality adjusted life year

[redacted]

Figure 15 Tornado diagram - nirsevimab vs maternal immunisation – Model 1

Figure 16 Tornado diagram - nirsevimab vs SoC - Model 2

12.2.2 Scenarios

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base case model(s) (Refer to Table 58 and Table 59). Influential factors for estimating the ICER of treatment with nirsevimab include e.g. the assumptions regarding the duration of the intervention season as well as the coverage rate for maternal immunisation. Considering that a NMA on efficacy has been conducted, this is considered as the most appropriate data source for efficacy, however, it has been explored whether a decrease in the coverage rate would impact the results. Furthermore, the duration of the intervention season is considered influential in both models, exploring whether the duration of the interventions would impact the ICER results is shown in the table below.

Table 58 Scenarios results – Model 1 (maternal immunisation)

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0%	NA	[redacted]	[redacted]	[redacted]
Duration of intervention season – 5 months	[redacted]	Alternative season duration	[redacted]	[redacted]	[redacted]
Number of bed days (for "åben indlæggelse") – 3 days	[redacted]	Alternate estimate. Assumption	[redacted]	[redacted]	[redacted]
Overall mortality	[redacted]	Using overall population risk of RSV-mortality	[redacted]	[redacted]	[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		(from RSV Dashboard			
Maternal immunisation coverage rate – Term infants = 50%	[redacted]	Alternate coverage rate assumption, based on previous pertussis seasons.	[redacted]	[redacted]	[redacted]

Abbreviations: DKK= Danish Krone, ICER= Incremental cost-effectiveness ratio, QALY= Quality adjusted life year, RSV= Respiratory syncytial virus

Table 59 Scenarios results – Model 2 (SoC)

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	0	NA	[redacted]	[redacted]	[redacted]
Duration of intervention season – 5 months	[redacted]	Alternative season duration	[redacted]	[redacted]	[redacted]
Number of bed days (for "åben indlæggelse") – 3 days	[redacted]	Alternate estimate. Assumption	[redacted]	[redacted]	[redacted]
Overall mortality	[redacted]	Alternate assumption on disease related mortality	[redacted]	[redacted]	[redacted]

Abbreviations: DKK= Danish Krone, ICER= Incremental cost-effectiveness ratio, QALY= Quality adjusted life year, RSV= Respiratory syncytial virus

12.2.3 Probabilistic sensitivity analyses

The PSA simultaneously varied all parameters with uncertainty in the model, sampling various input parameters from the appropriate probability distributions. A scatter plot of 1,000 simulations derived from model 1 and model 2 is presented in Figure 17 and Figure 18, respectively. Figure 19 and Figure 20 presents the cost-effectiveness acceptability curves derived from model 1 and model 2, respectively. The full set of parameters included in the model (including details of distributional forms) and the PSA analysis are presented in Appendix G. Refer to Appendix M for Scatter plot and CEAC curve presentation by subgroup

Figure 17 Scatter plot - nirsevimab vs maternal immunisation – Model 1

Figure 18 Scatter plot - nirsevimab vs SoC - Model 2

Figure 19 CEAC - nirsevimab vs maternal immunisation – Model 1

Figure 20 CEAC - nirsevimab vs SoC - Model 2

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending nirsevimab for the treatment of RSV in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. As the model results are based on one season (1 year), the budget impact results appear therefore "undiscounted". Patient cost and transportation cost have not been included as per DMC guidelines. The analysis is developed by comparing the costs for the Danish regions per year over five years, in the scenario where nirsevimab is recommended and the scenario where nirsevimab is not recommended. The total budget impact per year is the difference between the two scenarios.

13.1 Number of patients (including assumptions on market share)

Assuming all infants will receive nirsevimab, Table 2 presents the estimated number of eligible infants between 2024 and 2028, based on population projections from Statistics Denmark. Refer to Section 3.2 for further information. That said, the proportion of patients receiving nirsevimab is expected to change over time due to several factors (births, season etc). To estimate the budget impact of the introduction of nirsevimab, a starting prevalence population is based on the following subgroup (listed below) and adjusted based on expected patient numbers (Table 2):

- Preterm infants who are palivizumab eligible (<29wGA)
- Preterm infants that are not eligible for palivizumab (between 29wGA and 34wGA)
- Term infants (after 35wGA)

Table 60 Percentage of total births, by subgroup

	%	N (Year 1)	N (Year 2)	N (Year 3)	N (Year 4)	N (Year 5)
Palivizumab eligible infants	0.17%	107.56	113.35	116.43	121.04	124.05
Preterm infants	2.64%	1645.65	1734.26	1781.45	1851.84	1897.95
Term infants	97.18%	60485.79	63742.39	65477.11	68064.13	69759.00

Abbreviation: HCRU= health care resource use, N= numbers

Source: Esundhed.dk

Table 61 and Table 62 below present the numbers of treatment eligible patients expected to be treated over the next 5 years if nirsevimab is introduced against maternal immunisation and standard of care, respectively.

13.1.1 Market uptake

Number of expected infants eligible for treatment is estimated based on a 100% market uptake if nirsevimab is recommended, and 0% if nirsevimab is not recommended.

- For maternal immunisation, the number of expected infants eligible for treatment is estimated based on a 0% market uptake if nirsevimab is

recommended, and 0% (palivizumab eligible infants) and 100% in preterm and term infants if nirsevimab is not recommended.

- For SoC, the number of expected infants eligible for treatment is estimated based on a 0% market uptake if nirsevimab is recommended, and 100% (palivizumab eligible infants) and 0% in preterm and term infants if nirsevimab is not recommended.

Table 61 Number of new patients expected to be treated over the next five-year period if nirsevimab is introduced (adjusted for market share) – against maternal immunisation

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Nirsevimab					
Palivizumab eligible infants	108	113	116	121	124
Preterm infants	1646	1734	1781	1852	1898
Term infants	60486	63742	65477	68064	69759
Maternal immunisation					
Palivizumab eligible infants	0	0	0	0	0
Preterm infants	0	0	0	0	0
Term infants	0	0	0	0	0
			Non-recommendation		
Nirsevimab					
Palivizumab eligible infants	0	0	0	0	0
Preterm infants	0	0	0	0	0
Term infants	0	0	0	0	0
Maternal immunisation					
Palivizumab eligible infants	0	0	0	0	0
Preterm infants	1646	1734	1781	1852	1898
Term infants	60486	63742	65477	68064	69759

Table 62 Number of new patients expected to be treated over the next five-year period if nirsevimab is introduced (adjusted for market share) – against SoC

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Nirsevimab					
Palivizumab eligible infants	108	113	116	121	124
Preterm infants	1646	1734	1781	1852	1898
Term infants	60486	63742	65477	68064	69759
SoC					
Palivizumab eligible infants	0	0	0	0	0
Preterm infants	0	0	0	0	0
Term infants	0	0	0	0	0
			Non-recommendation		
Nirsevimab					

	Year 1	Year 2	Year 3	Year 4	Year 5
Palivizumab eligible infants	0	0	0	0	0
Preterm infants	0	0	0	0	0
Term infants	0	0	0	0	0
SoC					
Palivizumab eligible infants	108	113	116	121	124
Preterm infants	0	0	0	0	0
Term infants	0	0	0	0	0

Abbreviations: SoC= standard of care

13.2 Budget impact

The budget impact is informed by comparing the costs for the Danish healthcare system per year over five years in the scenario where nirsevimab is recommended as standard treatment and the scenario where nirsevimab is not recommended as standard treatment. The total budget impact per year is the difference between the two scenarios. The budget impact estimated is based cost outputs (2024 DKK) from the cost-effectiveness model for five years (assuming a constant yearly cost estimated from season 1), and the assumed eligible patients described above, as well as the assumed uptake of nirsevimab for the treatment of eligible infants. Table 63 and Table 64 present the budget impact of recommending nirsevimab against maternal immunisation and SoC, respectively.

Table 63 Expected budget impact of recommending nirsevimab against maternal immunisation

Vs Maternal immunisation	Year 1	Year 2	Year 3	Year 4	Year 5
Nirsevimab is recommended					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nirsevimab is NOT recommended					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64 Expected budget impact of recommending nirsevimab against SoC

Vs Maternal immunisation	Year 1	Year 2	Year 3	Year 4	Year 5
Nirsevimab is recommended					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nirsevimab is NOT recommended					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation					
Palivizumab eligible infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Preterm infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Term infants	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC= standard of care

14. List of experts

[redacted]

15. References

1. European Medicines Agency. Summary of Product Characteristics - Synagis.
2. Anne-Cathrine Viuff, Christina Schmidt, Dorthe Maria Vittrup, et al. Dansk Pædiatrisk Selskab - RSV Profylakse 2023.
3. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *New England journal of medicine* 2023; **388**(16): 1451-64.
4. European Medicines Agency. Summary of Product Characteristics - Abrysvo. 2023.
5. Jepsen MT, Trebbien R, Emborg HD, et al. Incidence and seasonality of respiratory syncytial virus hospitalisations in young children in Denmark, 2010 to 2015. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2018; **23**(3).
6. Garegnani L, Styrmisdóttir L, Roson Rodriguez P, Escobar Liquitay CM, Esteban I, Franco JVA. Palivizumab for preventing severe respiratory syncytial virus (RSV) infection in children. *Cochrane Database of Systematic Reviews* 2021; (11).
7. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *N Engl J Med* 2022; **386**(9): 837-46.

8. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *N Engl J Med* 2020; **383**(5): 415-25.
9. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *New England journal of medicine* 2023; **389**(26): 2425-35.
10. Simões EAF, Tita ATN, Swanson KA, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *New England journal of medicine* 2022; **386**(17): 1615-26.
11. Nielsen JP, Jacobsen T. RSV- profylakse med Palivisumab (Synagis) Dansk Pædiatrisk Selskab, 2018.
12. Statistics Denmark. Population projections. https://www.statistikbanken.dk/statbank5a/default.asp?w=27522024).
13. CDC. RSVin Infants and Youg Children. 2018. https://www.cdc.gov/rsv/high-risk/infants-young-children.html (accessed 09/01/2020.
14. Popow-Kraupp T, Aberle JH. Diagnosis of respiratory syncytial virus infection. *Open Microbiol J* 2011; **5**(SPEC. ISSUE 2): 128-34.
15. Centers for Disease Control and Prevention. RSV in Infants and Young Children. December 18 2020. https://www.cdc.gov/rsv/high-risk/infants-young-children.html (accessed June 29 2021).
16. Carvajal JJ, Avellaneda AM, Salazar-Ardiles C, Maya JE, Kalergis AM, Lay MK. Host Components Contributing to Respiratory Syncytial Virus Pathogenesis. *Front Immunol* 2019; **10**: 2152.
17. Heylen E, Neyts J, Jochmans D. Drug candidates and model systems in respiratory syncytial virus antiviral drug discovery. *Biochemical Pharmacology* 2017; **127**: 1-12.
18. Broberg EK, Waris M, Johansen K, Snacken R, Penttinen P, European Influenza Surveillance N. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2018; **23**(5).
19. Openshaw PJM, Chiu C, Culley FJ, Johansson C. Protective and Harmful Immunity to RSV Infection. *Annu Rev Immunol* 2017; **35**: 501-32.
20. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis* 2009; **9**(5): 291-300.
21. Piedimonte G, Perez MK. Respiratory syncytial virus infection and bronchiolitis. *Pediatrics in review* 2014; **35**(12): 519-30.
22. American Academy of Pediatrics. Respiratory Syncytial Virus. In: Pediatrics AAo, ed. Red Book: 2021–2024 Report of the Committee on Infectious Diseases; 2021: 628-36.
23. Fauroux B, Simoes EAF, Checchia PA, et al. The Burden and Long-term Respiratory Morbidity Associated with Respiratory Syncytial Virus Infection in Early Childhood. *Infect Dis Ther* 2017; **6**(2): 173-97.
24. Ledbetter J, Brannman L, Wade SW, Gonzales T, Kong AM. Healthcare resource utilization and costs in the 12 months following hospitalization for respiratory syncytial virus or unspecified bronchiolitis among infants. Supplementary material. *Journal of medical economics* 2020; **23**(2): 139-47.
25. Palmer L, Hall CB, Katkin JP, et al. Healthcare costs within a year of respiratory syncytial virus among medicaid infants. *Pediatr Pulmonol* 2010; **45**(8): 772-81.
26. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022; **399**(10340): 2047-64.
27. Centers for Disease Control and Prevention. RSV Transmission. 2020. https://www.cdc.gov/rsv/about/transmission.html (accessed 25 February 2022).

28. Thomas E, Mattila JM, Lehtinen P, Vuorinen T, Waris M, Heikkinen T. Burden of Respiratory Syncytial Virus Infection During the First Year of Life. *J Infect Dis* 2021; **223**(5): 811-7.
29. Yamin D, Jones FK, DeVincenzo JP, et al. Vaccination strategies against respiratory syncytial virus. *Proc Natl Acad Sci U S A* 2016; **113**(46): 13239-44.
30. Vandini S, Biagi C, Lanari M. Respiratory Syncytial Virus: The Influence of Serotype and Genotype Variability on Clinical Course of Infection. *Int J Mol Sci* 2017; **18**(8).
31. Collins PL, Graham BS. Viral and host factors in human respiratory syncytial virus pathogenesis. *Journal of virology* 2008; **82**(5): 2040-55.
32. Smith DK, Seales S, Budzik C. Respiratory Syncytial Virus Bronchiolitis in Children. *Am Fam Physician* 2017; **95**(2): 94-9.
33. Rankin DA, Haddadin Z, Lipworth L, et al. Comparison of Clinical Presentations and Burden of Respiratory Syncytial Virus in Infants Across Three Distinct Healthcare Settings. IDWeek 2020; 2020 October 21-25; Virtual; 2020.
34. Chatterjee A, Mavunda K, Krilov LR. Current State of Respiratory Syncytial Virus Disease and Management. *Infectious diseases and therapy* 2021; **10**(Suppl 1): 5-16.
35. Pickles RJ, DeVincenzo JP. Respiratory syncytial virus (RSV) and its propensity for causing bronchiolitis. *J Pathol* 2015; **235**(2): 266-76.
36. American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014; **134**(5): e1474-502.
37. Caballero MT, Polack FP. Respiratory syncytial virus is an "opportunistic" killer. *Pediatric pulmonology* 2018; **53**(5): 664-7.
38. Haddadin Z, Rankin DA, Lipworth L, et al. Clinical Characteristics of common Respiratory Viruses Detected in Infants Across Different Clinical Settings. IDWeek 2020; 2020 October 21-25; Virtual; 2020.
39. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010; **375**(9725): 1545-55.
40. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001; **344**(25): 1917-28.
41. Calvo C, Garcia-Garcia ML, Blanco C, et al. Multiple simultaneous viral infections in infants with acute respiratory tract infections in Spain. *J Clin Virol* 2008; **42**(3): 268-72.
42. Mansbach JM, Piedra PA, Teach SJ, et al. Prospective multicenter study of viral etiology and hospital length of stay in children with severe bronchiolitis. *Arch Pediatr Adolesc Med* 2012; **166**(8): 700-6.
43. Jensen A, Simoes EAF, Bohn Christiansen C, Graff Stensballe L. Respiratory syncytial virus and influenza hospitalizations in Danish children 2010-2016. *Vaccine* 2021; **39**(30): 4126-34.
44. Statens Serum Institut. RSV Dashboard. 2024. https://experience.arcgis.com/experience/220fef27d07d438889d651cc2e00076c/page/RS-virus/2024).
45. Ayieko P, English M. In Children Aged 2–59 months with Pneumonia, Which Clinical Signs Best Predict Hypoxaemia? *Journal of Tropical Pediatrics* 2006; **52**(5): 307-10.
46. Schauer U, Hoffjan S, Bittscheidt J, et al. RSV bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. *European respiratory journal* 2002; **20**(5): 1277-83.
47. Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic Accuracy of Rapid Antigen Detection Tests for Respiratory Syncytial Virus Infection: Systematic Review and Meta-analysis. *Journal of Clinical Microbiology* 2015; **53**(12): 3738-49.
48. Sundhedsstyrelsen, Lægemiddelstyrelsen, Statens Serum Institut. Årsrapport - Børnevaccinationsprogrammet 2023. 2024.

49. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--summary. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2011; **17 Suppl 6**: 1-24.
50. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Pediatr Infect Dis J* 2011; **30**(6): 510-7.
51. European Medicines Agency. Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease, 2018.
52. Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. *The Lancet Public health* 2017; **2**(8): e367-e74.
53. Demont C, Petrica N, Bardoulat I, et al. Economic and disease burden of RSV-associated hospitalizations in young children in France, from 2010 through 2018. *BMC Infect Dis* 2021; **21**(1): 730.
54. Reeves RM, Hardelid P, Panagiotopoulos N, Minaji M, Warburton F, Pebody R. Burden of hospital admissions caused by respiratory syncytial virus (RSV) in infants in England: A data linkage modelling study. *J Infect* 2019; **78**(6): 468-75.
55. Kieffer A, Beuvelet M, Sardesai A, et al. Expected Impact of Universal Immunization With Nirsevimab Against RSV-Related Outcomes and Costs Among All US Infants in Their First RSV Season: A Static Model. *J Infect Dis* 2022; **226**(Supplement_2): S282-s92.
56. Martinón-Torres F, Carmo M, Platero L, et al. Clinical and economic burden of respiratory syncytial virus in Spanish children: the BARI study. *BMC Infect Dis* 2022; **22**(1): 759.
57. Arriola CS, Kim L, Langley G, et al. Estimated Burden of Community-Onset Respiratory Syncytial Virus–Associated Hospitalizations Among Children Aged <2 Years in the United States, 2014–15. Supplementary material. *Journal of the Pediatric Infectious Diseases Society* 2019.
58. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics* 2013; **132**(2): e341-e8.
59. Arriola CS, Kim L, Langley G, et al. Estimated Burden of Community-Onset Respiratory Syncytial Virus-Associated Hospitalizations Among Children Aged <2 Years in the United States, 2014-15. *J Pediatric Infect Dis Soc* 2019.
60. Rha B, Curns AT, Lively JY, et al. Respiratory Syncytial Virus-Associated Hospitalizations Among Young Children: 2015-2016. *Pediatrics* 2020; **146**(1).
61. Ghazaly M, Nadel S. Characteristics of children admitted to intensive care with acute bronchiolitis. *European Journal of Pediatrics* 2018; **177**(6): 913-20.
62. Gantenberg JR, van Aalst R, Zimmerman N, et al. Medically Attended Illness due to Respiratory Syncytial Virus Infection Among Infants Born in the United States Between 2016 and 2020. *J Infect Dis* 2022; **226**(Suppl 2): S164-s74.
63. Kobayashi Y, Togo K, Agosti Y, McLaughlin JM. Epidemiology of respiratory syncytial virus in Japan: A nationwide claims database analysis. *Pediatr Int* 2022; **64**(1): e14957.
64. Hartmann K, Liese JG, Kemmling D, et al. Clinical Burden of Respiratory Syncytial Virus in Hospitalized Children Aged ≤5 Years (INSPIRE Study). *J Infect Dis* 2022; **226**(3): 386-95.
65. Yu J, Liu C, Xiao Y, et al. Respiratory Syncytial Virus Seasonality, Beijing, China, 2007-2015. *Emerg Infect Dis* 2019; **25**(6): 1127-35.

66. Reeves RM, Hardelid P, Gilbert R, et al. Epidemiology of laboratory-confirmed respiratory syncytial virus infection in young children in England, 2010-2014: the importance of birth month. *Epidemiol Infect* 2016; **144**(10): 2049-56.
67. Sanofi. Data on File. Linked Clinical Practice Research Datalink (CPRD) - Hospital Episode Statistics (HES) study to identify the burden of respiratory syncytial virus (RSV) in hospitalised children under 2 years of age, 2022.
68. Hall CB. The burgeoning burden of respiratory syncytial virus among children. *Infectious disorders drug targets* 2012; **12**(2): 92-7.
69. Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. *PloS one* 2013; **8**(2): e54445.
70. National Institute of Infectious Disease. RSV infection cases reported weekly (2008-2018), 2010.
71. Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, et al. Respiratory Syncytial Virus Seasonality: A Global Overview. *J Infect Dis* 2018; **217**(9): 1356-64.
72. Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *The Lancet Global Health* 2019; **7**(8): e1031-e45.
73. Rose EB, Wheatley A, Langley G, Gerber S, Haynes A. Respiratory syncytial virus seasonality - United States, 2014-2017, 2018.
74. Statens Serum Institut. Annual reports on disease incidence. 2023. https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-denmark/annual-reports-on-disease-incidence/influenza-2022-2023#:~:text=Respiratory%20syncytial%20virus%20(RSV),-Prior%20to%20COVID&text=The%20virus%20appeared%20in%20the,of%202022%20(Figure%208).
75. Simões E, et al.,. Pooled efficacy of nirsevimab against RSV lower respiratory tract infection in preterm and term infants. ESPID 2022 Congress; 2022 May 9-13, 2022; Hybrid Congress; 2022.
76. IMpact RSV Group. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* 1998; **102**(3): 531-7.
77. Stewart DL, Ryan KJ, Seare JG, Pinsky B, Becker L, Frogel M. Association of RSV-related hospitalization and non-compliance with Palivizumab among commercially insured infants: A retrospective claims analysis. *BMC Infect Dis* 2013; **13**(1).
78. Krilov LR, Masaquel AS, Weiner LB, Smith DM, Wade SW, Mahadevia PJ. Partial palivizumab prophylaxis and increased risk of hospitalization due to respiratory syncytial virus in a medicaid population: A retrospective cohort analysis. *BMC Pediatr* 2014; **14**(1): 1-11.
79. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023; **388**(16): 1451-64.
80. AstraZeneca. Data on File. Nirsevimab Draft Summary of Product Characteristics, 2022.
81. European Medicines Agency. Summary of Product Characteristics - Beyfortus. 2023.
82. World Health Organization. WHO preferred product characteristics of monoclonal antibodies for passive immunization against respiratory syncytial virus (RSV) disease, 2021.
83. Zhang XL, Zhang X, Hua W, et al. Expert consensus on the diagnosis, treatment, and prevention of respiratory syncytial virus infections in children. *World J Pediatr* 2024; **20**(1): 11-25.
84. Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. *New England journal of medicine* 2020; **383**(5): 415-25.

85. Domachowske J, Madhi SA, Simões EAF, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. *New England journal of medicine* 2022; **386**(9): 892-4.
86. Mao Z, Li X, Dacosta-Urbieta A, et al. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. *Vaccine* 2023; **41**(16): 2707-15.
87. Li X, Bilcke J, Fernández LV, et al. Cost-effectiveness of Respiratory Syncytial Virus Disease Prevention Strategies: Maternal Vaccine Versus Seasonal or Year-Round Monoclonal Antibody Program in Norwegian Children. *J Infect Dis* 2022; **jiac064**.
88. Sanofi. Data on RSV hospitalisations from Danish registries [Data on file]. 2024.
89. Statistics Denmark. BEV3A: Levendefødte og døde på måneder. 2024. www.statistikbanken.dk/BEV3A.
90. eSundhed. Nyfødte og fødsler (1997-); Graviditet: Graviditetslængde (niveau 2). 2024. https://www.esundhed.dk/Emner/Graviditet-foedsler-og-boern/Nyfoedte-og-foedsler-1997-.
91. Mira-Iglesias A, Demont C, Lopez-Labrador FX, et al. Role of age and birth month in infants hospitalized with RSV-confirmed disease in the Valencia Region, Spain. *Influenza Other Respir Viruses* 2022; **16**(2): 328-39.
92. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. *Pediatrics* 2013; **132**(2): e341-8.
93. Feltes TF, Simoes E. Palivizumab prophylaxis in haemodynamically significant congenital heart disease. *Arch Dis Child* 2005; **90**(8): 875-7; author reply -7.
94. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. *Pediatrics* 1998; **102**(3 Pt 1): 531-7.
95. Arriola CS, Kim L, Langley G, et al. Estimated Burden of Community-Onset Respiratory Syncytial Virus-Associated Hospitalizations Among Children Aged <2 Years in the United States, 2014-15. *J Pediatric Infect Dis Soc* 2020; **9**(5): 587-95.
96. Simoes EAF, Madhi SA, Muller WJ, et al. 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. *Lancet Child Adolesc Health* 2023; **7**(3): 180-9.
97. Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2024; **29**(4).
98. Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *The Lancet Infectious Diseases* 2024.
99. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. *New England journal of medicine* 2022; **386**(9): 837-46.
100. Blanken MO, Rovers MM, Molenaar JM, et al. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *N Engl J Med* 2013; **368**(19): 1791-9.
101. Tavsu I, Gursoy T, Dirman S, Erbil N, Ovali F. Palivizumab prophylaxis: does it have any influence on the growth and development of the infants? *Am J Perinatol* 2014; **31**(8): 667-72.
102. Subramanian KS, Weisman LE, Rhodes T, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *The Pediatric infectious disease journal* 1998; **17**(2): 110-5.

103. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003; **143**(4): 532-40.
104. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database Syst Rev* 2013; (4): CD006602.
105. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. *Eurosurveillance* 2024; **29**(6): 2400046.
106. Ares-Gómez S, Mallah N, María-Isolina S-P, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. *Lancet Infectious diseases/˜The œLancet Infectious diseases* 2024.
107. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *N Engl J Med* 2023; **389**(26): 2425-35.
108. Balduzzi S, Rücker G, Nikolakopoulou A, et al. netmeta: An R Package for Network Meta-Analysis Using Frequentist Methods. *Journal of Statistical Software* 2023; **106**(2).
109. Simoes EAF, Center KJ, Tita ATN, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *N Engl J Med* 2022; **386**(17): 1615-26.
110. European Medicines Agency. Abrysvo - Public assessment report. 2023.
111. Weigl M, Schneider A, Hoffmann F, Angerer P. Work stress, burnout, and perceived quality of care: a cross-sectional study among hospital pediatricians. *European Journal of Pediatrics* 2015; **174**(9): 1237-46.
112. Simoes EAF, Madhi SA, Llapur CJ, et al. Establishing Proof of Concept for a Bivalent RSVpreF Subunit Vaccine for Maternal Immunization. *Open forum infectious diseases* 2022; **9**: S13.
113. EUCTR. A TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF A RESPIRATORY SYNCYTIAL VIRUS (RSV) PREFUSION F SUBUNIT VACCINE IN INFANTS BORN TO WOMEN VACCINATED DURING PREGNANCY. *https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2019-002943-85-DK* 2020.
114. Pfizer I. A Phase 3, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of a Respiratory Syncytial Virus (Rsv) Prefusion F Subunit Vaccine in Infants Born to Women Vacci.
115. Sundhedsstyrelsen. Erfaringsopsamling - Læringer fra udrulning af

sæsonvaccinationsprogrammer 2022-2023. 2023.
116. Nygaard U, Hartling UB, Nielsen J, et al. Hospital admissions and need for mechanical ventilation in children with respiratory syncytial virus before and during the COVID-19 pandemic: a Danish nationwide cohort study. *Lancet Child Adolesc Health* 2023; **7**(3): 171-9.
117. Lively JY, Curns AT, Weinberg GA, et al. Respiratory Syncytial Virus-Associated Outpatient Visits Among Children Younger Than 24 Months. *J Pediatric Infect Dis Soc* 2019; **8**(3): 284-6.
118. Li X, Hodgson D, Flaig J, et al. Cost-Effectiveness of Respiratory Syncytial Virus Preventive Interventions in Children: A Model Comparison Study. *Value Health* 2023; **26**(4): 508-18.
119. Escobar GJ, Masaquel AS, Li SX, Walsh EM, Kipnis P. Persistent recurring wheezing in the fifth year of life after laboratory-confirmed, medically attended respiratory syncytial virus infection in infancy. *BMC pediatrics* 2013; **13**: 97.
120. Shi T, Ooi Y, Zaw EM, et al. Association Between Respiratory Syncytial Virus-Associated Acute Lower Respiratory Infection in Early Life and Recurrent Wheeze and Asthma in Later Childhood. *J Infect Dis* 2020; **222**(Suppl 7): S628-S33.

121. Centers for Disease Control and Prevention. National Vital System: Deaths: Final Data for 2015. 2017. https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf (accessed October 2021.
122. AstraZeneca. MELODY - Clinical Study Report [Data on file], 2023.
123. MedImmune. D5290C00003 - Clinical Study Report [Data on file], 2019.
124. Sanofi Pasteur. Clinical Study Report - VAS00006 HARMONIE [Data on file], 2023.
125. Mao Z, Li X, Dacosta-Urbieta A, et al. Economic burden and health-related quality-of-life among infants with respiratory syncytial virus infection: A multi-country prospective cohort study in Europe. *Vaccine* 2023; **41**(16): 2707-15.
126. Willems DC, Joore MA, Hendriks JJ, Wouters EF, Severens JL. Cost-effectiveness of a nurse-led telemonitoring intervention based on peak expiratory flow measurements in asthmatics: results of a randomised controlled trial. *Cost Eff Resour Alloc* 2007; **5**: 10.
127. Hodgson D, Atkins KE, Baguelin M, et al. Estimates for quality of life loss due to Respiratory Syncytial Virus. *Influenza Other Respir Viruses* 2020; **14**(1): 19-27.
128. Díez-Gandía E, Gómez-Álvarez C, López-Lacort M, et al. The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain. *BMC Infect Dis* 2021; **21**(1): 924.
129. Hodgson D, Atkins KE, Baguelin M, et al. Estimates for quality of life loss due to Respiratory Syncytial Virus. *Influenza and other respiratory viruses* 2020; **14**(1): 19-27.
130. Statistics Denmark. Life expectancy. 2024. https://www.dst.dk/en/Statistik/emner/borgere/befolkning/middellevetid.
131. Tarride JE, Burke N, Bischof M, et al. A review of health utilities across conditions common in paediatric and adult populations. *Health Qual Life Outcomes* 2010; **8**: 12.
132. Danish Medicines Council. The Danish Medicines Council methods guide for assessing new pharmaceuticals v1.2, 2021.
133. Danish Medicines Council. Værdisætning af enhedsomkostninger, 2023.
134. Lægemiddelstyrelsen. Medicinpriser.dk. 2024. https://medicinpriser.dk/.
135. NCT. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended RSV LRTI in Healthy Late Preterm and Term Infants. *https://clinicaltrialsgov/show/NCT05238974* 2022.
136. AstraZeneca. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended Lower Respiratory Tract Infection Due to Respiratory Syncytial Virus in Healthy Late Preterm and Term Infants (MELODY). 2021.
137. MedImmune LLC. A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of MEDI8897, a Monoclonal Antibody With an Extended Half-life Against Respiratory Syncytial Virus, i.
138. Muller WJ, Madhi SA, Seoane Nunez B, et al. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. *New England Journal of Medicine* 2023; **388**(16): 1533-4.
139. Ahani B, Tuffy KM, Aksyuk AA, et al. Molecular and phenotypic characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. *Nature communications* 2023; **14**(1): 4347.
140. Dagan R, Hammitt LL, Seoane Nunez B, et al. Infants Receiving a Single Dose of Nirsevimab to Prevent RSV Do Not Have Evidence of Enhanced Disease in their Second RSV Season. *J Pediatric Infect Dis Soc* 2024; **14**: 14.
141. Hammitt L, Dagan R, Yuan Y, et al. The Efficacy and Impact in Heathy Infants of Nirsevimab on Medically Attended RSV Lower Respiratory Tract Infection. *Open forum infectious diseases* 2021; **8**(SUPPL 1): S811-S2.
142. MedImmune LLC. A Study to Evaluate the Safety and Efficacy of MEDI8897 for the Prevention of Medically Attended RSV LRTI in Healthy Preterm Infants. 2018.
143. Madhi SA, Simões EAF. Single-dose nirsevimab prevents RSV infection. *Journal of pediatrics* 2021; **228**: 310-3.
144. Griffin MP, Yuan Y, Takas T, et al. MEDI8897 prevents serious RSV disease in healthy preterm infants. *Open forum infectious diseases* 2019; **6**: S27.

145. EUCTR. Clinical Study to Evaluate the Safety and Efficacy of MEDI8897, an Experimental Drug, for Preventing Serious Respiratory Syncytial Virus Disease in Healthy Preterm Infants. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2016-001677-33-HU 2016.
146. Sanofi Pasteur aSC, AstraZeneca, Sanofi. Study of a Single Intramuscular Dose of Nirsevimab in the Prevention of Hospitalizations Due to Respiratory Syncytial Virus (RSV) Infection in Healthy Term and Preterm Infants During the First Year of Life. 2024.
147. EUCTR. Study of a single intramuscular dose of nirsevimab in the prevention of hospitalizations due to respiratory syncytial virus (RSV) infection in healthy term and preterm infants during the first year of life. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2022-000099-20-DE 2022.
148. Sanofi P. A Phase IIIb randomized open-label study of nirsevimab (versus no intervention) in preventing hospitalizations due to respiratory syncytial virus in infants (HARMONIE).
149. Rucker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012; **3**(4): 312-24.
150. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023): Cochrane; 2023.
151. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.
152. Ren L, Cui L, Wang Q, et al. Cost and health-related quality of life for children hospitalized with respiratory syncytial virus in Central China. *Influenza Other Respir Viruses* 2023; **17**(8): e13180.
153. Wrotek A, Wrotek O, Jackowska T. The Impact of RSV Hospitalization on Children's Quality of Life. *Diseases* 2023; **11**(3).
154. Reeves RM, van Wijhe M, Tong S, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. *J Infect Dis* 2020; **222**(Suppl 7): S599-S605.
155. Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, et al. Burden of Respiratory Syncytial Virus in the European Union: estimation of RSV-associated hospitalizations in children under 5 years. *J Infect Dis* 2023; **228**(11): 1528-38.
156. Johannesen CK, van Wijhe M, Tong S, et al. Age-Specific Estimates of Respiratory Syncytial Virus-Associated Hospitalizations in 6 European Countries: A Time Series Analysis. *J Infect Dis* 2022; **226**(Suppl 1): S29-S37.
157. Lamb A, Murray A, Lovett R. The Challenges of Measuring and Valuing Quality of Life in Preschool Children: A Retrospective Review of NICE Appraisals. *Children (Basel)* 2021; **8**(9).
158. AstraZeneca. MEDLEY - Clinical Study Report (Data on file), 2023.

Appendix A. Main characteristics of studies included

Table 65 Main characteristic of studies included - MELODY

Trial name: MELODY	NCT number: NCT03979313
Objective	To evaluate the efficacy, safety, pharmacokinetics (PK), and antidrug antibody (ADA) response for nirsevimab in healthy late preterm and term infants who are 35 weeks or greater gestational age and entering their first RSV season.

Trial name: MELODY	NCT number: NCT03979313
Publications – title, author, journal, year	Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. New England journal of medicine 2022; 386(9): 837-46.[7]
Study type and design	Double-blinded, randomised, placebo-controlled phase 3 study. Infants were randomised 2:1 to either nirsevimab or placebo. Randomization was stratified according to hemisphere of residence (northern or southern) and age (≤3.0 months, >3.0 to 6.0 months, or >6.0 months). Participants, care providers, investigators, and outcome assessors were masked to treatment assignment.
Sample size (n)	N = 3012
Main inclusion criteria	• Healthy infants in their first year of life and born at or after 35 weeks 0 days GA • Infants who are entering their first RSV season at the time of screening
Main exclusion criteria	• Meets national or other local criteria to receive commercial palivizumab • Any fever (≥ 100.4°F [≥ 38.0°C], regardless of route) or acute illness within 7 days prior to randomization • Active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing) or known prior history of RSV infection • Receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine, including maternal RSV vaccination
Intervention	One intramuscular injection of nirsevimab (at a dose of 50 mg if they weighed <5 kg or at a dose of 100 mg if they weighed ≥5 kg) n = 2,009
Comparator(s)	Placebo n = 1,003
Follow-up time	Efficacy: 150 days after injection Safety: Last in-person visit 361 days after injection. Follow-up by telephone 511 days after injection
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint:** - Number of Participants With MA RSV LRTI Through 150 Days Post Dose (Primary Cohort)

Trial name: MELODY	NCT number: NCT03979313
	Secondary endpoints: - Number of Participants With MA RSV LRTI With Hospitalisation Through 150 Days Post Dose (Primary Cohort) - Summary of Serum Concentrations (ug/mL) of MEDI8897 by Group - Anti-drug Antibody Results by Visit (As Treated Population) - Number of Participants With MA RSV LRTI Through 150 Days Post Dose (All Subjects) - Number of Participants With MA RSV LRTI With Hospitalisation Through 150 Days Post Dose (All Subjects) - Number of Participants With Disease From the 2nd RSV Season (All Subjects)
Method of analysis	All efficacy analyses were intent-to-treat analyses. The relative risk reduction of participants with MA RSV LRTI and MA RSV LRTI hospitalisation was analyses using Poisson regression with robust variance (stratified by age at randomisation) obtained after multiple imputation.
Subgroup analyses	No subgroup analyses are presented in this submission. The following sub-group analyses were pre-specified: • Hemisphere of residence • Age at randomisation • Sex • Race • Weight • Gestational age
Other relevant information	*N/A*

Table 66. Main characteristics of studies included – Griffin et al. 2020

Trial name: Griffin et al. 2020	NCT number: NCT02878330
Objective	To evaluate the efficacy, safety, pharmacokinetics (PK), and antidrug antibody (ADA) response for MEDI8897 in healthy preterm infants who are between 29 and 35 weeks gestational age (GA) and entering their first Respiratory Syncytial Virus (RSV) season.
Publications – title, author, journal, year	Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. New England journal of medicine 2020; 383(5): 415-25.[84]

Trial name: Griffin et al. 2020	NCT number: NCT02878330
Study type and design	A phase 2, randomised, quadruple-blind, placebo-controlled trial. Participants, care-providers, investigators, and outcomes-assessor were blinded to treatment assignment.
Sample size (n)	N = 1453
Main inclusion criteria	• Healthy infants born between 29 weeks 0 days and 34 weeks 6 days GA. • Infants who are entering their first full RSV season at the time of screening.
Main exclusion criteria	• Meets American Academy of Pediatrics (AAP) or other local criteria to receive commercial palivizumab. • Any fever (>= 100.4°F [>= 38.0°C], regardless of route) or lower respiratory illness within 7 days prior to randomization. • Acute illness (defined as the presence of moderate or severe signs and symptoms) at the time of randomization. • Active RSV infection (a child with signs/symptoms of respiratory infection must have negative RSV testing) or known prior history of RSV infection. • Receipt of palivizumab or other RSV monoclonal antibody or any RSV vaccine, including maternal RSV vaccination.
Intervention	Nirsevimab 50 mg: Participants will receive a single IM dose of nirsevimab 50 milligrams (mg) on Day 1 of the study. n = 969
Comparator(s)	Placebo: Participants will receive a single intramuscular (IM) dose of placebo matched to nirsevimab on Day 1 of the study. n = 484
Follow-up time	Efficacy: 150 days after injection Safety: 360 days after injection
Is the study used in the health economic model?	Yes, the study is used in the NMA informing the prevention efficacy of nirsevimab and Abrysvo
Primary, secondary and exploratory endpoints	**Primary outcome:** - Number of Participants With Medically Attended Respiratory Syncytial Virus (RSV) Confirmed Lower Respiratory Tract Infection (LRTI). Time frame: From Day 1 through Day 151 **Secondary outcomes:**

Trial name: Griffin et al. 2020	NCT number: NCT02878330
	- Number of Participants Hospitalized Due to Respiratory Syncytial Virus (RSV) Confirmed Lower Respiratory Tract Infection (LRTI). Time frame: From Day 1 through Day 151 - Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs). Time frame: From Day 1 through Day 361 - Number of Participants With Adverse Events of Special Interest (AESIs) and New Onset Chronic Diseases (NOCDs). Time frame: From Day 1 through Day 361 - Serum Concentration of MEDI8897. Time frame: Days 91, 151, and 361 - Elimination Half-life (t1/2) of MEDI8897. Time frame: Day 91 through Day 361 - Number of Participants With Positive Anti-drug Antibodies to MEDI8897. Time frame: Days 91, 151, and 361
Method of analysis	All efficacy analyses were intent-to-treat analyses. The relative risk reduction of participants with MA RSV LRTI and MA RSV LRTI hospitalisation was analyses using Poisson regression with robust variance (stratified by age at randomisation) obtained after multiple imputation.
Subgroup analyses	No subgroup analyses are presented in this submission. The following sub-group analyses were pre-specified: • Hemisphere of residence • Age at randomisation • Sex • Race • Siblings (twins or triplets included in the trial) • Gestational age
Other relevant information	*N/A*

Table 67. Main characteristics of studies included - HARMONIE

Trial name: HARMONIE	NCT number: NCT05437510
Objective	To determine the efficacy and safety of a single intramuscular (IM) dose of nirsevimab, compared to no intervention, for the prevention of hospitalizations due to lower respiratory tract infection (LRTI) caused by confirmed RSV infection (henceforth referred to as RSV LRTI

Trial name: HARMONIE	NCT number: NCT05437510
	hospitalizations) in all infants under 12 months of age who are not eligible to receive palivizumab.
Publications – title, author, journal, year	Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *New England journal of medicine* 2023; **389**(26): 2425-35.[9]
Study type and design	A phase 3, randomised, open-label trial.
Sample size (n)	n = 8058
Main inclusion criteria	- Born at ≥ 29 weeks gestational age and aged 0 to 12 months (calendar age), who are entering their first RSV season on the day of inclusion in the study (D01) - Informed consent form has been signed and dated by the parent(s) or other LAR(s) (and by an independent witness if required by local regulations) - Participant and parent/LAR are able to attend the scheduled visit and to comply with all study procedures
Main exclusion criteria	- Participants are not eligible for the study if any of the following criteria are met: - Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months) - Active confirmed RSV infection at the time of dosing/randomization - Active LRTI at the time of dosing/randomization - Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study intervention used in the study or to a product containing any of the same substances - Laboratory confirmed thrombocytopenia, or known thrombocytopenia, as reported by the parent/LAR, contraindicating intramuscular injection - Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular injection - Any condition that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion - Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 38.0°C \[≥ 100.4°F\]) on the day of study intervention administration.

Trial name: HARMONIE	NCT number: NCT05437510
	- A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided - Mother of the infant participant was administered an RSV vaccine during her pregnancy with the infant participant - Receipt of any monoclonal antibody by the infant participant - Receipt of immune globulins, blood or blood-derived products in the past 3 months by the infant participant - Participation at the time of study enrolment or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure - Eligible to receive palivizumab at time of inclusion (as per local guidelines) - In an emergency setting or hospitalized involuntarily - Identified as a natural or adopted child of the Investigator or employee with direct involvement in the proposed study The above information was not intended to contain all considerations relevant to a participant's potential participation in a clinical trial.
Intervention	Nirsevimab: 1 intramuscular injection at Day 01 n = 4037
Comparator(s)	No preventive intervention for RSV: No intervention n = 4021
Follow-up time	**Efficacy:** up to 180 days post randomisation **Safety:** up to 1 year post randomisation
Is the study used in the health economic model?	Yes, the study is included in the NMA informing the efficacy of nirsevimab versus Abrysvo
Primary, secondary and exploratory endpoints	**Primary outcome:** - Overall incidence of RSV LRTI hospitalization through the RSV season. Time frame: Up to 180 days post-dosing/randomization **Secondary outcomes:** - Incidence of very severe RSV LRTI through the RSV season. Time frame: Up to 180 days post-dosing/randomization - Incidence of hospitalization for LRTI through the RSV season in each country. Time frame: Up to 180 days post-dosing/randomization

Trial name: HARMONIE	NCT number: NCT05437510

- Overall hospitalization for all cause LRTI in all 3 countries combined throughout the RSV season. Time frame: Up to 180 days post-dosing/randomization

- Incidence (overall and in each country) of RSV LRTI hospitalization throughout 150 days post-dosing/randomization. Time frame: Day 151

- Incidence of very severe RSV LRTI in all 3 countries combined through 150 days post-dosing/randomization. Time frame: Day 151

- Incidence of hospitalizations for all cause LRTI through 150 days post-dosing/randomization. Time frame: Day 151

- Incidence of RSV LRTI hospitalization throughout the second year post-immunization/randomization. Time frame: Day 366 to Day 731

- Incidence of hospitalizations for all-cause LRTI throughout the second-year post immunization/randomization. Time frame: Day 366 to Day 731

- Any immediate adverse events (AEs) reported in the 30◦minutes after immunization. Time frame: 30 minutes after immunization

- Non-serious AEs from D01 (post-dosing/randomization) to D31. Time frame: Day 01 to Day 31

- Adverse events of special interest (AESIs) from D01 visit through 1-year post-dosing/randomization or D366. Time frame: Day 01 through 1-year post-dosing/randomization (Day 366)

- Medically attended adverse events (MAAEs) from D01 visit through 1-year post-dosing/randomization or D366. Time frame: Day 01 through 1-year post-dosing/randomization (Day 366)

- Serious adverse events (SAEs) from D01 visit through 1-year post-dosing/randomization or D366. Time frame: Day 01 through 1-year post-dosing/randomization (Day 366)

- Related SAEs from D366 to D731 for United Kingdom (UK) participants. Time frame: Day 366 to D 731

- Incidence of RSV LRTI hospitalizations through 180 days post-dosing/randomization (overall and in each country). Time frame: Day 01 through 180 days post-dosing/randomization

- Incidence of hospitalizations for all cause LRTI through 180 days post-dosing/randomization. Time frame: Day 01 through 180 days post-dosing/randomization

- Incidence of RSV LRTI hospitalization from 181 days post-dosing/randomization until D366 the end of the study (overall and in each country). Time frame: 181 days post-dosing/randomization until Day 366

- Incidence of hospitalizations for all cause LRTI from 181 days post-dosing/randomization until D366. Time frame: 181 days post-dosing/randomization until Day 366

Trial name: HARMONIE	NCT number: NCT05437510
	- Incidence of recurrent wheeze in UK reconsented participants from D01 to D731. Time frame: Day 01 to Day 731"
Method of analysis	All efficacy analyses were done using the ITT population. Efficacy analyses were done using the exact method with binomial distribution.
Subgroup analyses	No subgroup analyses are presented in this submission. The following sub-group analyses were pre-specified: • Timing of randomisation (before or during RSV season) • Age at randomisation • Sex • Race • Weight • Gestational age
Other relevant information	*N/A*

Table 68. Main characteristics of included studies - MEDLEY

Trial name: MEDLEY	NCT number: NCT03959488
Objective	To evaluate the safety and tolerability of MEDI8897 compared to palivizumab when administered to preterm infants entering their first RSV season and children with chronic lung disease (CLD) and congenital heart disease (CHD) entering their first and second RSV season.
Publications – title, author, journal, year	Domachowske J, Madhi SA, Simões EAF, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. N Engl J Med 2022; 386(9): 892-4.
Study type and design	A phase2, phase3, randomised, quadruple-blind, placebo-controlled trial. Participants, care-providers, investigators, and outcomes-assessor were blinded to treatment assignment.
Sample size (n)	n = 925
Main inclusion criteria	1. Any fever (≥ 100.4°F \[≥ 38.0°C\], regardless of route) or acute illness within 7 days prior to randomization 2. Any history of LRTI or active LRTI prior to, or at the time of, randomization 3. Known history of RSV infection or active RSV infection prior to, or at the time of, randomization

Trial name: MEDLEY	NCT number: NCT03959488
	4. Hospitalization at the time of randomization, unless discharge is expected within the 7 days after randomization 5. Requirement for mechanical ventilation, extracorporeal membrane oxygenation, CPAP, or other mechanical respiratory or cardiac support at the time of randomization 6. Anticipated cardiac surgery within 2 weeks after randomization 7. Anticipated survival of \< 6 months after randomization 8. Receipt of any investigational drug 9. Known renal impairment 10. Known hepatic dysfunction including known or suspected active or chronic hepatitis infection 11. Clinically significant congenital anomaly of the respiratory tract 12. Chronic seizure, or evolving or unstable neurologic disorder 13. Prior history of a suspected or actual acute life-threatening event 14. Known immunodeficiency, including human immunodeficiency virus (HIV) 15. Mother with HIV infection (unless the child has been proven to be not infected) 16. Any known allergy, including to immunoglobulin products, or history of allergic reaction 17. Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination 18. Receipt of any monoclonal or polyclonal antibody (for example, hepatitis B immune globulin, intravenous immunoglobulin) or anticipated use during the study 19. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of subject safety or study results 20. Concurrent enrolment in another interventional study 21. Children of employees of the sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals
Main exclusion criteria	1. Any fever (≥ 100.4°F \[≥ 38.0°C\], regardless of route) or acute illness within 7 days prior to randomization 2. Any history of LRTI or active LRTI prior to, or at the time of, randomization 3. Known history of RSV infection or active RSV infection prior to, or at the time of, randomization

Trial name: MEDLEY	NCT number: NCT03959488
	4. Hospitalization at the time of randomization, unless discharge is expected within the 7 days after randomization 5. Requirement for mechanical ventilation, extracorporeal membrane oxygenation, CPAP, or other mechanical respiratory or cardiac support at the time of randomization 6. Anticipated cardiac surgery within 2 weeks after randomization 7. Anticipated survival of \< 6 months after randomization 8. Receipt of any investigational drug 9. Known renal impairment 10. Known hepatic dysfunction including known or suspected active or chronic hepatitis infection 11. Clinically significant congenital anomaly of the respiratory tract 12. Chronic seizure, or evolving or unstable neurologic disorder 13. Prior history of a suspected or actual acute life-threatening event 14. Known immunodeficiency, including human immunodeficiency virus (HIV) 15. Mother with HIV infection (unless the child has been proven to be not infected) 16. Any known allergy, including to immunoglobulin products, or history of allergic reaction 17. Receipt of palivizumab or other RSV mAb or any RSV vaccine, including maternal RSV vaccination 18. Receipt of any monoclonal or polyclonal antibody (for example, hepatitis B immune globulin, intravenous immunoglobulin) or anticipated use during the study 19. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of subject safety or study results 20. Concurrent enrolment in another interventional study 21. Children of employees of the sponsor, clinical study site, or any other individuals involved with the conduct of the study, or immediate family members of such individuals
Intervention	MEDI8897: anti-RSV monoclonal antibody with an extended half-life N = 614
Comparator(s)	Palivizumab: anti-RSV monoclonal antibody N = 304
Follow-up time	360 days post first dose

Trial name: MEDLEY	NCT number: NCT03959488
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary outcome: - Safety and Tolerability of MEDI8897 as Assessed by the Occurrence of All Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs) and Adverse Events of Special Interest (AESIs) and New Onset Chronic Disease (NOCD). Time frame: 360 days post first dose Secondary outcomes: - Serum Concentrations of MEDI8897 and Palivizumab. Time frame: Day 15, Day 31, Day 151 post first dose in Season 1 and Season 2 - Incidence of Anti-drug Antibody (ADA) to MEDI8897 and Palivizumab in Serum. Time frame: 360 days post first dose - Incidence of Medically Attended Lower Respiratory Track Infection (LRTI) and Hospitalization Due to Reverse Transcriptase Chain Reaction (RT-PCR) Confirmed Respiratory Syncytial Virus (RSV) Through 150 Days Post First Dose. Time frame: 150 days post first dose
Method of analysis	No hypothesis testing was conducted as part of the MEDLEY study. Outcomes were assessed using descriptive statistics
Subgroup analyses	The study population was divided into the preterm cohort, and a cohort of children with CLD or hemodynamically significant CHD.
Other relevant information	

Table 69. Main characteristics of included studies - Simoes et al. 2022

Trial name: Simoes et al. 2022	NCT number: NCT04032093
Objective	To evaluate the safety, tolerability, and immunogenicity of an RSV vaccine in pregnant participants who receive either one of 2 dose levels of the vaccine, formulated with or without aluminium hydroxide, or placebo, and investigate safety and characteristics of antibodies in their infants.
Publications – title, author, journal, year	Simoes EAF, Center KJ, Tita ATN, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. N Engl J Med 2022; 386(17): 1615-26.

Trial name: Simoes et al. 2022	NCT number: NCT04032093
Study type and design	A phase 2, randomised, quadruple-blind, placebo-controlled trial. Participants, care-providers, investigators, and outcomes-assessor were blinded to treatment assignment.
Sample size (n)	n = 1153
Main inclusion criteria	**Inclusion Criteria - Maternal participants:** - Healthy women 18 to 49 years of age between 24 and 36 weeks of gestation on the day of planned vaccination, with an uncomplicated pregnancy, who are at no known increased risk for complications, and whose foetus has no significant abnormalities observed on ultrasound. - Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. - Receiving prenatal standard of care. - Had an ultrasound performed at \>=18 weeks of pregnancy. - Had a negative urinalysis for protein and glucose at the screening visit. Trace protein in the urine is acceptable if the blood pressure is also normal. - Determined by medical history, physical examination, screening laboratory assessment, and clinical judgment to be appropriate for inclusion in the study. - Documented negative human immunodeficiency virus antibody, hepatitis B virus surface antigen, hepatitis C virus antibody, and syphilis tests at the screening visit. - Body mass index of \</=40 kg/m2 at the time of the screening visit. - Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent document and in this protocol. - Expected to be available for the duration of the study and willing to give informed consent for her infant to participate in the study. **Inclusion Criteria - Infant Participants:** - Evidence of a signed and dated ICD signed by the parent(s). - Parent(s) willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
Main exclusion criteria	**Exclusion Criteria - Maternal Participants:** - Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. - History of severe adverse reaction associated with a vaccine and/or severe allergic reaction to any component of the investigational product or any related vaccine.

- History of latex allergy.

- History of any severe allergic reaction.

- Participants with known or suspected immunodeficiency.

- Current pregnancy resulting from in vitro fertilization or other assisted reproductive technology.

- A prior history of or known current pregnancy complications or abnormalities that will increase the risk associated with the participant's participation in and completion of the study.

- Major illness of the mother or conditions of the foetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response.

- Participant with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention including but not limited to systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).

- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

- Participation in other studies involving investigational drug(s) within 28 days prior to study entry and/or during study participation.

- Participants who receive treatment with immunosuppressive therapy including cytotoxic agents or systemic corticosteroids (such as for cancer or an autoimmune disease), or planned receipt of such treatment or agents during study participation. If systemic corticosteroids have been administered short term (\<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before investigational product administration.
Inhaled/nebulized, intra articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

- Current alcohol abuse or illicit drug use.

- Receipt of blood or plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (e.g., RhoGAM), which can be given at any time.

Trial name: Simoes et al. 2022	NCT number: NCT04032093
	- Previous vaccination with any licensed or investigational RSV vaccine or planned receipt during study participation. - Laboratory test results at the screening visit outside the normal reference value for pregnant women according to their trimester in pregnancy. - Participants who are breastfeeding at the time of the screening visit. **Exclusion Criteria - Infant Participants:** - Infant who is a direct descendant (e.g., child or grandchild) of the study personnel.
Intervention	Abrysvo, 120µg, without adjuvant N = 79 infants Abrysvo, 120µg, with aluminium hydroxide N = 84 infants Abrysvo, 240µg, without adjuvant N = 77 infants Abrysvo, 240µg, with aluminium hydroxide N = 78
Comparator(s)	Placebo dose: Normal saline solution for injection (0.9% sodium chloride injection) N = 78
Follow-up time	Safety: up to one year after birth Efficacy (post-hoc): From September 2019 to May 2020
Is the study used in the health economic model?	Yes, the study is included in the NMA informing the efficacy of Nirsevimab versus placebo and Abrysvo
Primary, secondary and exploratory endpoints	**Primary outcomes:** - Percentage of Maternal Participants With Prespecified Local Reactions by Maximum Severity Within 7 Days After Vaccination. Time frame: Within 7 days after vaccination - Percentage of Maternal Participants With Prespecified Systemic Events by Maximum Severity Within 7 Days After Vaccination. Time frame: Within 7 days after vaccination - Percentage of Maternal Participants With Adverse Events (AEs) Within 1 Month After Vaccination. Time frame: Within 1 month after vaccination - Percentage of Maternal Participants With Serious Adverse Events (SAEs), Medically Attended Adverse Events (MAEs) and Obstetric

Trial name: Simoes et al. 2022	NCT number: NCT04032093
	Complications. Time frame: From day of vaccination (Day 1) up to 12 months post-delivery - Percentage of Infant Participants With Specific Birth Complications. Time frame: At birth - Percentage of Infant Participants With Any AE Within 1 Month of Age. Time frame: Within 1 month after birth - Percentage of Infant Participants With MAEs and SAEs Within 12 Months of Age. Time frame: Within 12 months after birth - Percentage of Infant Participants With AEs of Special Interest of at Least Moderate Severity Within 12 Months of Age: Congenital Anomalies and Developmental Delay. Time frame: Within 12 months after birth **Secondary outcomes:** - Geometric Mean Titer (GMT) of Respiratory Syncytial Virus Subgroup A (RSV A) and Subgroup B (RSV B) Neutralizing Antibodies in Maternal Participants. Time frame: Before vaccination, 2 weeks and 1 month after vaccination and at delivery - Geometric Mean Fold Rise (GMFR) for Respiratory Syncytial Virus Subgroup A (RSV A) and Subgroup B (RSV B) Neutralizing Antibody Titers in Maternal Participants. Time frame: 2 weeks and 1 month after vaccination, at delivery - Geometric Mean Titer (GMT) of Respiratory Syncytial Virus Subgroup A (RSV A) and Subgroup B (RSV B) Neutralizing Antibodies in Infant Participants. Time frame: At birth and at 1, 2, 4, 6 months after birth
Method of analysis	No formal hypothesis testing was done. All outcomes were described using descriptive statistics.
Subgroup analyses	None
Other relevant information	*N/A*

Table 70. Main characteristics of included studies - MATISSE

Trial name: MATISSE	NCT number: NCT04424316
Objective	To evaluate the efficacy and safety of maternal immunization with RSVpreF against medically attended lower respiratory tract illness (MA-LRTI) in infants.

Trial name: MATISSE	NCT number: NCT04424316
Publications – title, author, journal, year	Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med 2023; 388(16): 1451-64.
Study type and design	A phase3, randomised, quadruple-blind, placebo-controlled trial. Participants, care-providers, investigators, and outcomes-assessor were blinded to treatment assignment.
Sample size (n)	n = 7,128 infants
Main inclusion criteria	**Inclusion Criteria - Maternal Participants:** - Healthy women ≤49 years of age who are between 24 0/7 and 36 0/7 weeks of gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, who are at no known increased risk for complications. - Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. - Receiving prenatal standard of care based on country requirements. - Had a foetal anomaly ultrasound examination performed at ≥18 weeks of pregnancy with no significant fetal abnormalities observed. - Determined by medical history, physical examination, and clinical judgment to be appropriate for inclusion in the study. - Documented negative HIV antibody test, syphilis test, and hepatitis B virus (HBV) surface antigen test during this pregnancy and prior to randomization (Visit 1). - Intention to deliver at a hospital or birthing facility where study procedures can be obtained. - Expected to be available for the duration of the study and can be contacted by telephone during study participation. - Participant is willing to give informed consent for her infant to participate in the study. - Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol OR If the maternal participant is illiterate, a thumbprinted informed consent must be obtained, which must be signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant has been informed of all pertinent aspects of the study. **Inclusion Criteria -Infant Participants:** - Evidence of a signed and dated ICD signed by the parent(s)/legal guardian(s) OR If the infant participant's maternal participant/parent(s)/legal guardian(s) is illiterate, a thumbprinted informed consent must have been obtained, which must have been

Trial name: MATISSE	NCT number: NCT04424316
	signed and dated by an impartial witness who was present throughout the entire informed consent process confirming that the maternal participant/parent(s)/legal guardian(s) has been informed of all pertinent aspects of the study for herself (maternal participant) and her foetus/infant prior to taking part in the study. - Parent(s)/legal guardian(s) willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
Main exclusion criteria	**Exclusion Criteria - Maternal Participants:** - Prepregnancy body mass index (BMI) of \>40 kg/m2. If prepregnancy BMI is not available, the BMI at the time of the first obstetric visit during the current pregnancy may be used. - Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection. - History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the investigational product or any related vaccine. - Current pregnancy resulting from in vitro fertilization. - Current pregnancy complications or abnormalities at the time of consent that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: - Preeclampsia, eclampsia, or uncontrolled gestational hypertension. - Placental abnormality. - Polyhydramnios or oligohydramnios. - Significant bleeding or blood clotting disorder. - Endocrine disorders, including untreated hyperthyroidism or untreated hypothyroidism. This also includes disorders of glucose intolerance (e.g., diabetes mellitus type 1 or 2) antedating pregnancy or occurring during pregnancy if uncontrolled at the time of consent. - Any signs of premature labour with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth. - Prior pregnancy complications or abnormalities at the time of consent, based on the investigator's judgment, that will increase the risk associated with the participation in and completion of the study, including but not limited to the following: - Prior preterm delivery ≤34 weeks' gestation. - Prior stillbirth or neonatal death. - Previous infant with a known genetic disorder or significant congenital anomaly.

- Major illness of the maternal participant or conditions of the foetus that, in the investigator's judgment, will substantially increase the risk associated with the maternal or infant participant's participation in, and completion of, the study or could preclude the evaluation of the maternal participant's response (includes positive serologic testing for regional endemic conditions assessed during routine maternal care, as per local standards of care and obstetric recommendations).

- Congenital or acquired immunodeficiency disorder, or rheumatologic disorder or other illness requiring chronic treatment with known immunosuppressant medications, including monoclonal antibodies, within the year prior to enrolment.

- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

- Participation in other studies involving investigational drug(s) within 28 days prior to consent and/or during study participation.

- Receipt of monoclonal antibodies within the year prior to enrolment or the use of systemic corticosteroids for \>14 days within 28 days prior to study enrolment. Permitted treatments include the receipt of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies, prednisone doses of \<20 mg/day for ≤14 days and, inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids.

- Current alcohol abuse or illicit drug use. Note: Marijuana use is not considered an exclusion criterion for the study when elicited in participant screening, though it may be considered illicit in some locales.

- Receipt of blood or plasma products or immunoglobulin (Ig), from 60 days before investigational product administration, or planned receipt through delivery, with 1 exception, Rho(D) immune globulin (e.g., RhoGAM), which can be given at any time.

- Previous vaccination with any licensed or investigational RSV vaccine or planned. Note: Licensed COVID-19 vaccines or COVID-19 vaccines authorized for temporary or emergency use will not be prohibited during the course of this study.

- Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

- Participants who are breastfeeding at the time of enrolment.

Exclusion Criteria -Infant Participants:

Trial name: MATISSE	NCT number: NCT04424316
	- Infant who is a direct descendant (e.g., child or grandchild) of the study personnel.
Intervention	Abrysvo N = 3570 infants
Comparator(s)	Placebo N = 3558
Follow-up time	Efficacy: up to one year post birth Safety: up to two years post birth
Is the study used in the health economic model?	Yes the study is used in the NMA informing the efficacy of nirsevimab versus maternal immunisation and placebo
Primary, secondary and exploratory endpoints	**Primary outcomes:** - The percentage reduction in the incidence of medically attended LRTI (MA-LRTI) due to RSV in infants through 180 days of life. Time frame: Delivery to 180 days after delivery - The percentage reduction in the incidence of medically attended severe LRTI due to RSV in infants through 180 days of life. Time frame: Delivery to 180 days after delivery - The percentage of infant participants with specific birth outcomes. Time frame: Birth - The percentage of infant participants with adverse events (AEs) from birth to 1 month of age. Time frame: Up to 1 month of age - The percentage of infant participants with serious adverse events (SAE) and newly diagnosed chronic medical conditions (NDCMCs) from birth to 12 months of age. Time frame: From birth up to 12 months of age - The percentage of infant participants with serious adverse events (SAE) and newly diagnosed chronic medical conditions (NDCMCs) from birth to 24 months of age. Time frame: From birth up to 24 months of age - Percentage of maternal participants reporting local reactions and systemic events from day of vaccination (Day 1) until Day 7. Time frame: From day of vaccination until 7 days after vaccination - Percentage of maternal participants reporting Adverse Events (AE) within 1 month after vaccination. Time frame: Within 1 month after vaccination - Percentage of maternal participants reporting SAEs. Time frame: From enrolment up to 180 days after delivery **Secondary outcomes:**

Trial name: MATISSE	NCT number: NCT04424316
	- The percentage reduction in the incidence of hospitalizations due to RSV in infants through 360 days of life. Time frame: Delivery to 360 days after delivery - The percentage reduction in the incidence of all-cause MA-LRTI in infant participants. Time frame: Delivery to 360 days after delivery - The percentage reduction in the incidence of MA-LRTI due to RSV in infants participants. Time frame: Delivery to 360 days after delivery
Method of analysis	Safety was described descriptively All efficacy analyses were done using the evaluable population. The evaluable population consisted of all infant participants who were eligible, were born to the maternal participants who had received the randomly assigned vaccine or placebo at least 14 days before delivery, did not receive palivizumab or another monoclonal antibody targeting RSV, had no major protocol violations, and had not received transfusions (of any blood products) of more than 20 ml per kilogram of body weight within 180 days after birth. Vaccine efficacy, estimated with the use of the binomial distribution of the number of cases of disease in the RSV vaccine group and given the total number of cases in both groups,27 was defined as (1–RR)×100, where RR is the relative risk of the end point of interest based on the incidence in the vaccine group as compared with the placebo group. A lower boundary of the confidence interval that was greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points, and a lower boundary of 0% was considered to meet the success criterion for vaccine efficacy with respect to the secondary end points
Subgroup analyses	None reported
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Table 71 Results per MELODY

Results of MELODY (NCT03979313)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MA RSV LRTI (Primary Cohort)	Nirsevimab	994	12 (1.2)	Not calculated			Relative risk reduction: 74.53	49.63 to 87.12	<0.0001	Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance (including stratification factor [age at randomisation] as covariate) obtained after missing data imputation.	Clinicaltrials.gov
	Placebo	496	25 (5.0%)								
MA RSV LRTI (All subjects)	Nirsevimab	2009	24 (1.2%)	Not calculated			Relative risk reduction: 76.36	62.27 to 85.18	<0.0001	Relative risk reduction of nirsevimab vs placebo, 95% CI and the nominal p-value were estimated based on Poisson regression with robust variance (including stratification factors [hemisphere and age at randomisation and cohort] as covariates) obtained after missing data imputation.	Clinicaltrials.gov
	Placebo	1003	54 (5.4%)								

Results of MELODY (NCT03979313)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MA RSV LRTI Hospitalisation (Primary cohort)	Nirsevimab	994	6 (0.6%)	Not calculated			Relative risk reduction: 62.15	-8.57 to 86.80	0.0708	Relative risk reduction of Medi8897 versus placebo; 95% CI and p-value estimated with Poisson regression with robust variance (including stratification factors [age at randomisation] as covariate) obtained after multiple imputation	Clinicaltrials.gov
	Placebo	496	8 (1.6%)								
MA RSV LRTI Hospitalisation (All subjects cohort)	Nirsevimab	2009	9 (0.4%)	Not calculated			Relative risk reduction: 76.84	49.36 to 89.41	0.0002	Relative risk reduction of Medi8897 versus placebo; 95% CI and p-value estimated with Poisson regression with robust variance (including stratification factors [age at randomisation] as covariate) obtained after multiple imputation	Clinicaltrials.gov
	Placebo	1003	20 (2.0%)								

Table 72. Results per Griffin et al. 2020

Results of Griffin et al. 2020 (NCT02878330)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
MA RSV LRTI	Nirsevimab	969	25 (2.6%)	Not calculated			Relative risk reduction: 70.1	52.3 to 81.2	<0.0001	The determination of medically attended RSV LRTI is based on objective clinical LRTI criteria and RSV test results obtained from analysing the respiratory secretions using a validated RSV real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay for the detection of RSV A or RSV B subtypes. Criteria for LRTI included documented physical exam findings of rhonchi, rales, crackles, or wheeze and any of the following: increased respiratory rate at rest (for age less than (<) 2 months: greater than or equal to (>=) 60 breaths/min; 2-6 months: >= 50 breaths/min; and for > 6 months - 2 years, >= 40 breaths/min), or hypoxemia (in room air - oxygen saturation < 95% at altitudes less than or equal to (<=) 1800 meters or < 92% at altitudes > 1800 meters), or clinical signs of severe respiratory disease or dehydration secondary to inadequate	Clinicaltrials.gov Griffin et al. 2020[8]

Results of Griffin et al. 2020 (NCT02878330)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Placebo	484	46 (9.5%)							oral intake due to respiratory distress (need for intravenous fluid). Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance after missing data imputation.	
MA RSV LRTI Hospitalisations	Nirsevimab	969	8 (0.8%)	Not calculated			Relative risk reduction: 78.4	51.9 to 90.3	<0.0002	A RSV hospitalization is defined as either 1) a respiratory hospitalization with a positive RSV test within 2 days of hospitalization (primary) or 2) new onset of respiratory symptoms in an already hospitalized child, with an objective measure of	Griffin et al. 2020[8]
	Placebo	484	20 (4.1%)								

Results of Griffin et al. 2020 (NCT02878330)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										worsening respiratory status and positive RSV test (nosocomial). Relative risk reduction of nirsevimab vs placebo, the 95% CI and p-value were estimated based on Poisson regression with robust variance after missing data imputation.	

Table 73. Results per HARMONIE

Results of HARMONIE (NCT05437510)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Hospitalisation for RSV LRTI	Nirsevimab	4037	11 (0.3%)	Not calculated			83.2%	67.8% to 92.0%	<0.0001	Hospitalization for RSV-associated lower respiratory tract infection was defined as admission to the hospital on the basis of the treating physician's decision and confirmation of RSV by means of a	Drysdale et al. 2023[107]2023[107]
	No intervention	4021	60 (1.5%)								

Results of HARMONIE (NCT05437510)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										positive result of a test performed in accordance with routine practice, during the RSV season in France, Germany, and the United Kingdom.	
Very severe RSV-associated lower respiratory tract infection	Nirsevimab	4037	5 (0.1%)	Not calculated			75.7%	32.8% to 92.9%	0.0004	Very severe RSV associated lower respiratory tract infection was defined as hospitalization for RSV-associated lower respiratory tract infection with an oxygen saturation <90 at any time during hospitalization and the need for supplemental oxygen	Drysdale et al. 2023[107]2023[107]
	No intervention	4021	19 (0.5%)								

Table 74. Results per Simoes et al. 2022

Results of Simoes et al 2022 (NCT04032093)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Any medically attended RSV-associated lower respiratory tract illness (Timeframe: Not reported)	Abrysvo	405	3 (0.7%)	Not calculated			Estimated vaccine efficacy: 84.7%	21.6 to 97.6%	Not reported	Any medically attended RSV-associated lower respiratory tract illness was defined as a medically attended visit (i.e., the infant participant was taken to or seen by a health care provider in an outpatient or inpatient visit, emergency department, or urgent care clinic, or in a home visit) and the presence of one of the following signs of RSV-associated lower respiratory tract illness: tachypnoea (respiratory rate ≥60 breaths per minute in infants younger than 2 months [60 days] of age or ≥50 breaths per minute in those 2 to 12 months of age); a peripheral capillary oxygen saturation as measured by pulse oximetry (SpO2) below 95% while the infant was breathing ambient air; and indrawing of the chest wall. Vaccine efficacy was estimated post hoc as the relative risk reduction in	Simoes et al. 2022[10]
	Placebo	103	5 (4.8%)								

Results of Simoes et al 2022 (NCT04032093)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										the combined RSVpreF vaccine groups as compared with the placebo group. Confidence intervals were calculated with the use of an exact conditional method based on binomial distribution	
Medically attended severe RSV-associated lower respiratory tract illness (Timeframe: not reported)	Abrysvo	405	1 (0.2%)	Not calculated			Estimated vaccine efficacy: 91.5%	-5.6% to 99.8%	Not reported	A medically attended severe RSV-associated lower respiratory tract illness was defined as a medically attended visit and the presence of one of the following signs of severe RSV-associated lower respiratory tract illness: tachypnoea (respiratory rate ≥70 breaths per minute in infants younger than 2 months [60 days] of age or ≥60 breaths per minute in those between 2 months and 12 months of age); SpO2 <93% while the infant was breathing ambient air; use of oxygen delivered through a high-flow nasal cannula or mechanical ventilation; admission to an intensive care unit for more than	Simoes et al. 2022[10]
	Placebo	103	3 (2.9%)								

Results of Simoes et al 2022 (NCT04032093)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										4 hours; and unresponsiveness or unconsciousness. Vaccine efficacy was estimated post hoc as the relative risk reduction in the combined RSVpreF vaccine groups as compared with the placebo group. Confidence intervals were calculated with the use of an exact conditional method based on binomial distribution	

Table 75. Results per MATISSE

Results of MATISSE (NCT04424316)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Medically attended severe	Abrysvo	3495	16 (0.5%)	Not calculated				44.5 to 85.9%	Not reported	Medically attended severe RSV-LRTI was defined as; A medically-attended visit AND ≥1 of the	Kampmann et al. 2023[3]

Results of MATISSE (NCT04424316)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
RSV-associated lower respiratory tract illness (Timeframe 150 days post birth*)	Placebo	3480	55 (1.6%)				Vaccine efficacy: 70.9%			following RTI signs and symptoms: Nasal discharge for ≥24 hours, Difficulty breathing, laboured breathing, or rapid breathing (any duration), Cough, Inability to feed for any duration because of respiratory symptoms, Apnoea, or Any other respiratory symptom of concern **AND** a RSV-positive-test-result **AND** ≥1 of the following: Fast breathing (RR ≥70 bpm for <2 months of age [<60 days of age], ≥60 bpm for 2–<12 months of age, or ≥50 bpm for 12–24 months of age), SpO2 <93%, High-flow nasal cannula or mechanical ventilation (i.e., invasive or non-invasive), ICU admission for >4 hours, or Failure to respond/unconscious Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness.	

Results of MATISSE (NCT04424316)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Cis were calculated as 97.58% CIs (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure	
Medically attended RSV-associated lower respiratory tract illness (Timeframe 150 days post birth*)	Abrysvo	3495	47 (1.3%)	Not calculated			Vaccine efficacy: 52.5%	(28.7% to 68.9%)	Not reported	Medically attended RSV-LRTI was defined as; A medically-attended visit AND ≥1 of the following RTI signs and symptoms: Nasal discharge for ≥24 hours, Difficulty breathing, laboured breathing, or rapid breathing (any duration), Cough, Inability to feed for any duration because of respiratory symptoms, Apnoea, Any other respiratory symptom of concern AND a RSV-positive-test-result Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness.	Kampmann et al. 2023[3]
	Placebo	3480	99 (2.8%)								

Results of MATISSE (NCT04424316)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										Cis were calculated as 97.58% CIs (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure	
Hospitalized RSV-RTI (Timeframe: 150 days post birth*)	Abrysvo	3495	17 (0.5%)	Not calculated			56.4%	5.2% to 81.5%	Not reported	Hospitalised RSV-RTI was defined as RTI due to RSV that results in hospitalization. Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using the Bonferroni procedure and accounting for the primary endpoints results. As a secondary endpoint, the criterion for vaccine efficacy was a lower bound of the confidence interval >0%	Kampmann et al. 2023[3]
	Placebo	3480	39 (1.1%)								

Appendix C. Comparative analysis of efficacy

To facilitate a comparison of nirsevimab versus maternal immunisation with Abrysvo, an indirect treatment comparison was carried out. As all trials shared a common comparator (placebo/no intervention), and trials were considered sufficiently similar to allow for indirect treatment comparison without population adjustment, a frequentist NMA was chosen as the appropriate method for indirect comparison.

This SLR included six studies reporting efficacy data for either nirsevimab or Abrysvo for the prevention of RSV in infants (three for nirsevimab and two for Abrysvo). A summary of trial design, populations, and efficacy outcomes is provided in Table 76.

Table 76. Design, population and outcomes of studies included in frequentist NMA

Trial	Study design	Population	Interventions	Efficacy outcomes
MELODY[99,135-141]MELODY[99,135-141]	Phase 3, randomised, double-blind, placebo-controlled study	Healthy late preterm and term infants (GA ≥ 35+0 weeks)	Nirsevimab (n=2009) Placebo (n=1003)	Number of participants with MA RSV LRTI (through 150 days post dose) Number of participants with MA RSV LRTI with hospitalisation (through 150 days post dose)
Griffin et al. 2020[84,139,142-145]2020[84,139,142-145]	Phase 2b, randomised, double-blind, placebo-controlled study	Healthy preterm infants (GA between 29+0 and 34+6 weeks)	Nirsevimab (n=969) Placebo (n=484)	Number of participants with MA RSV LRTI (from day 1 to day 151)
HARMONIE[9,146-148]HARMONIE[9,146-148]	Phase 3b, randomised, open-label study	Healthy term and preterm infants (GA ≥ 29+0 weeks)	Nirsevimab (n=4037) No intervention (n=4021)	Number of participants with MA RSV LRTI (from day 1 to day 151) Number of participants with MA RSV LRTI with hospitalisation

				(through 150 days post dose)
Simoes et al. 2022[10,112]	Phase 2b, randomised, placebo-controlled, observer-blinded trial	Infants born to healthy women 18-49 years of age, vaccinated between 24 and 36 weeks of gestation	Abrysvo (n=405) Placebo (n=103)	Number of participants with MA RSV LRTI (150 days post birth)
MATISSE[3,113,114]	Phase 3, randomised, double-blind, placebo-controlled trial	Infants born to healthy women under 49 years of age, vaccinated between 24+0 and 36+0 weeks of gestation	Abrysvo (n=3495) Placebo (480)	Number of participants with MA RSV LRTI (150 days post birth) Number of participants with MA RSV LRTI with hospitalisation (150 days post birth)

C.1 Methods of synthesis

C.1.1 Comparisons against placebo

For the comparisons of nirsevimab versus placebo, random-effects meta-analysis were conducted for the comparisons that were informed by multiple trials. The meta-analyses were fitted using the *metabin* function from the *meta* package in R. The default settings were used, meaning that in the random-effects meta-analysis the Mantel-Haenszel estimator is used in the calculation of the between-study heterogeneity, which is then used in the DerSimonian-Laird estimator. The random-effects estimate is based on the inverse variance method. The methods used are described in detail elsewhere{Schwarzer, 2015 #3909}.

C.1.2 Comparisons against Abrysvo

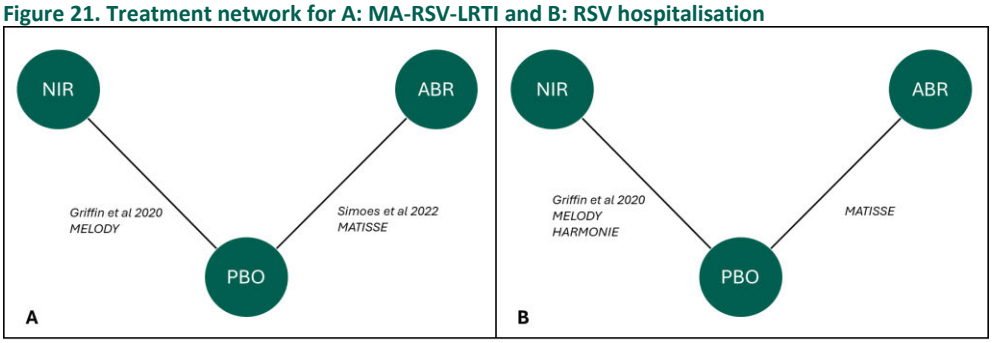
For the comparison against Abrysvo, the included studies were combined using frequentist NMA methodology as implemented in the *netmeta* package for R[108]. The detailed methods of the frequentist NMA are described in the paper accompanying the R package (Balduzzi et al. 2023) and will not be described in detail here.

The *netmeta* package adopts the approach proposed by Rücker, which relies on graph-theoretical methods[149].The *netmeta* package adopts the approach proposed by Rücker,

which relies on graph-theoretical methods[149]. As all outcomes included in the NMA were binary, random-effect models were fitted with the *netmetabin* package, using risk ratios (RR) as the summary measure. The pooling of study-specific estimates was done using the inverse-variance method, where more weight is given to studies with larger sample sizes and more precise estimates. For the random-effects model, the direct treatment estimates are based on the common between-study variance τ^2 from the network meta-analysis. The default estimator for τ^2 in the *netmeta* package, is a special case of the generalised DerSimonian-Laird estimate[108].

Within-design heterogeneity (i.e., heterogeneity between studies examining the same treatments, e.g., nirsevimab versus placebo) can be assessed using τ^2. Between-design heterogeneity can only be assessed when "closed loops" exist in the treatment network, i.e., when at least one comparison is informed by both direct and indirect evidence. As this is not the case for the treatment network employed here (shown in Figure 21) only within design heterogeneity was assessed.

Figure 21. Treatment network for A: MA-RSV-LRTI and B: RSV hospitalisation



Abbreviations: ABR= Abrysvo, NIR= nirsevimab, PBO= placebo/no intervention

Appendix D. Extrapolation

No extrapolation was done as part of the health economic modelling for this submission.

Appendix E. Serious adverse events

Table 77. Serious adverse events observed in MELODY

Adverse event	Nirsevimab (n = 1997)	Placebo (n = 997)
Hypochromic anaemia	1 (0.05%)	0 (0.00%)
Bronchogenic cyst	1 (0.05%)	0 (0.00%)
Phenylketonuria	0 (0.00%)	1 (0.10%)
Pyloric stenosis	1 (0.05%)	0 (0.00%)
Food poisoning	0 (0.00%)	1 (0.10%)
Gastritis	1 (0.05%)	0 (0.00%)
Gastroesophageal reflux disease	2 (0.10%)	0 (0.00%)
Impaired gastric emptying	1 (0.05%)	0 (0.00%)
Intestinal obstruction	0 (0.00%)	1 (0.10%)
Vomiting	1 (0.05%)	0 (0.00%)
Allergic colitis	1 (0.05%)	0 (0.00%)
Allergic gastroenteritis	0 (0.00%)	1 (0.10%)
Colitis	1 (0.05%)	1 (0.10%)
Constipation	0 (0.00%)	1 (0.10%)
Diarrhoea	3 (0.15%)	0 (0.00%)
Enteritis	1 (0.05%)	0 (0.00%)
Death	1 (0.05%)	0 (0.00%)
Fever neonatal	1 (0.05%)	1 (0.10%)
Pyrexia	6 (0.30%)	1 (0.10%)
Cholelithiasis	1 (0.05%)	0 (0.00%)
Jaundice	1 (0.05%)	0 (0.00%)
Milk allergy	1 (0.05%)	0 (0.00%)
Abscess limb	0 (0.00%)	1 (0.10%)
Abscess neck	1 (0.05%)	0 (0.00%)
Abscess of external auditory meatus	0 (0.00%)	1 (0.10%)
Adenoviral upper respiratory infection	3 (0.15%)	0 (0.00%)
Bacterial sepsis	0 (0.00%)	1 (0.10%)
Botulism	1 (0.05%)	0 (0.00%)
Bronchiolitis	27 (1.35%)	17 (1.71%)

Bronchitis	3 (0.15%)	4 (0.40%)
Bronchitis viral	1 (0.05%)	0 (0.00%)
Covid-19	3 (0.15%)	2 (0.20%)
Covid-19 pneumonia	1 (0.05%)	1 (0.10%)
Cellulitis	0 (0.00%)	1 (0.10%)
Conjunctivitis viral	1 (0.05%)	0 (0.00%)
Enterovirus infection	1 (0.05%)	0 (0.00%)
Escherichia pyelonephritis	1 (0.05%)	0 (0.00%)
Escherichia urinary tract infection	2 (0.10%)	0 (0.00%)
Exanthema subitum	1 (0.05%)	0 (0.00%)
Gastroenteritis	14 (0.70%)	5 (0.50%)
Gastroenteritis escherichia coli	0 (0.00%)	1 (0.10%)
Gastroenteritis adenovirus	0 (0.00%)	1 (0.10%)
Gastroenteritis clostridial	1 (0.05%)	0 (0.00%)
Gastroenteritis norovirus	0 (0.00%)	1 (0.10%)
Gastroenteritis rotavirus	2 (0.10%)	1 (0.10%)
Gastroenteritis viral	1 (0.05%)	0 (0.00%)
Hand-foot-and-mouth disease	1 (0.05%)	0 (0.00%)
Impetigo	1 (0.05%)	0 (0.00%)
Infection	1 (0.05%)	0 (0.00%)
Laryngitis	3 (0.15%)	3 (0.30%)
Lower respiratory tract infection	6 (0.30%)	0 (0.00%)
Lower respiratory tract infection viral	3 (0.15%)	1 (0.10%)
Nasopharyngitis	2 (0.10%)	0 (0.00%)
Otitis media	0 (0.00%)	2 (0.20%)
Otitis media acute	1 (0.05%)	0 (0.00%)
Pertussis	1 (0.05%)	0 (0.00%)
Pharyngotonsillitis	1 (0.05%)	0 (0.00%)
Pneumonia	13 (0.65%)	5 (0.50%)
Pneumonia aspiration	1 (0.05%)	0 (0.00%)
Pneumonia pneumococcal	1 (0.05%)	0 (0.00%)
Pneumonia respiratory syncytial viral	2 (0.10%)	1 (0.10%)
Pneumonia viral	2 (0.10%)	0 (0.00%)

Pyelonephritis	1 (0.05%)	0 (0.00%)
Respiratory syncytial virus bronchiolitis	5 (0.25%)	10 (1.00%)
Respiratory syncytial virus bronchitis	1 (0.05%)	2 (0.20%)
Staphylococcal abscess	1 (0.05%)	0 (0.00%)
Staphylococcal scalded skin syndrome	0 (0.00%)	1 (0.10%)
Streptococcal sepsis	1 (0.05%)	1 (0.10%)
Tonsillitis	0 (0.00%)	1 (0.10%)
Tracheobronchitis	0 (0.00%)	2 (0.20%)
Upper respiratory tract infection	4 (0.20%)	2 (0.20%)
Urinary tract infection	7 (0.35%)	5 (0.50%)
Urosepsis	1 (0.05%)	0 (0.00%)
Viral infection	2 (0.10%)	0 (0.00%)
Viral upper respiratory tract infection	4 (0.20%)	0 (0.00%)
Accidental exposure to product by child	0 (0.00%)	1 (0.10%)
Accidental overdose	1 (0.05%)	0 (0.00%)
Burns third degree	1 (0.05%)	0 (0.00%)
Concussion	0 (0.00%)	1 (0.10%)
Fall	1 (0.05%)	0 (0.00%)
Femur fracture	1 (0.05%)	0 (0.00%)
Hand fracture	1 (0.05%)	0 (0.00%)
Head injury	0 (0.00%)	1 (0.10%)
Skull fractured base	1 (0.05%)	0 (0.00%)
Thermal burn	0 (0.00%)	1 (0.10%)
Dairy intolerance	0 (0.00%)	1 (0.10%)
Decreased appetite	1 (0.05%)	0 (0.00%)
Dehydration	1 (0.05%)	1 (0.10%)
Failure to thrive	1 (0.05%)	0 (0.00%)
Food refusal	1 (0.05%)	0 (0.00%)
Hypoglycaemia	1 (0.05%)	0 (0.00%)
Scoliosis	0 (0.00%)	1 (0.10%)
Facial paralysis	0 (0.00%)	1 (0.10%)
Febrile convulsion	4 (0.20%)	0 (0.00%)

Hypotonia	1 (0.05%)	0 (0.00%)
Idiopathic generalised epilepsy	0 (0.00%)	1 (0.10%)
Seizure	2 (0.10%)	1 (0.10%)
Subarachnoid haemorrhage	1 (0.05%)	0 (0.00%)
Jaundice neonatal	1 (0.05%)	0 (0.00%)
Behavioural insomnia of childhood	1 (0.05%)	0 (0.00%)
Sleep terror	1 (0.05%)	0 (0.00%)
Staring	1 (0.05%)	0 (0.00%)
Apnoea	1 (0.05%)	0 (0.00%)
Aspiration	1 (0.05%)	0 (0.00%)
Bronchial hyperreactivity	1 (0.05%)	0 (0.00%)
Pneumonitis	1 (0.05%)	0 (0.00%)
Petechiae	1 (0.05%)	0 (0.00%)
Kawasaki's disease	2 (0.10%)	1 (0.10%)
Shock	1 (0.05%)	0 (0.00%)

Source: Clinicaltrials.gov

Notes: Infection-related AE account for all types of infections (including RSV)

Table 78. Serious adverse events observed in Griffin et al. 2020

Adverse event	Nirsevimab (n = 968)	Placebo (n = 479)
Anaemia neonatal	0 (0.00%)	1 (0.21%)
Cardiac arrest	1 (0.10%)	0 (0.00%)
Cardiac failure	1 (0.10%)	0 (0.00%)
Cardiac failure congestive	1 (0.10%)	0 (0.00%)
Myocarditis	0 (0.00%)	1 (0.21%)
Pericardial effusion	0 (0.00%)	1 (0.21%)
Muscular dystrophy	1 (0.10%)	0 (0.00%)
Deafness bilateral	1 (0.10%)	0 (0.00%)
Abdominal pain	1 (0.10%)	0 (0.00%)
Diarrhoea	2 (0.21%)	1 (0.21%)
Dysphagia	1 (0.10%)	0 (0.00%)
Enteritis	1 (0.10%)	1 (0.21%)
Gastroesophageal reflux disease	1 (0.10%)	0 (0.00%)
Incarcerated umbilical hernia	1 (0.10%)	0 (0.00%)
Inguinal hernia	1 (0.10%)	6 (1.25%)

Malabsorption	1 (0.10%)	0 (0.00%)
Vomiting	2 (0.21%)	0 (0.00%)
Death	1 (0.10%)	0 (0.00%)
Pyrexia	3 (0.31%)	1 (0.21%)
Jaundice	1 (0.10%)	0 (0.00%)
Drug hypersensitivity	1 (0.10%)	0 (0.00%)
Abscess limb	1 (0.10%)	0 (0.00%)
Adenovirus infection	0 (0.00%)	1 (0.21%)
Anal abscess	1 (0.10%)	0 (0.00%)
Bronchiolitis	20 (2.07%)	21 (4.38%)
Bronchitis	14 (1.45%)	11 (2.30%)
Croup infectious	2 (0.21%)	0 (0.00%)
Cytomegalovirus infection	0 (0.00%)	1 (0.21%)
Gastroenteritis	9 (0.93%)	4 (0.84%)
Gastroenteritis escherichia coli	0 (0.00%)	1 (0.21%)
Gastroenteritis adenovirus	1 (0.10%)	0 (0.00%)
Gastroenteritis rotavirus	0 (0.00%)	2 (0.42%)
Gastroenteritis salmonella	1 (0.10%)	1 (0.21%)
Gastroenteritis viral	1 (0.10%)	1 (0.21%)
Influenza	0 (0.00%)	1 (0.21%)
Laryngitis	1 (0.10%)	0 (0.00%)
Lower respiratory tract infection	14 (1.45%)	13 (2.71%)
Lower respiratory tract infection viral	5 (0.52%)	3 (0.63%)
Meningitis	0 (0.00%)	1 (0.21%)
Meningitis bacterial	0 (0.00%)	1 (0.21%)
Otitis media	2 (0.21%)	0 (0.00%)
Peritonsillar abscess	0 (0.00%)	1 (0.21%)
Pharyngitis	1 (0.10%)	0 (0.00%)
Pneumonia	13 (1.34%)	10 (2.09%)
Pneumonia bacterial	0 (0.00%)	1 (0.21%)
Pneumonia parainfluenzae viral	0 (0.00%)	1 (0.21%)
Pneumonia respiratory syncytial viral	2 (0.21%)	2 (0.42%)
Pneumonia viral	7 (0.72%)	2 (0.42%)

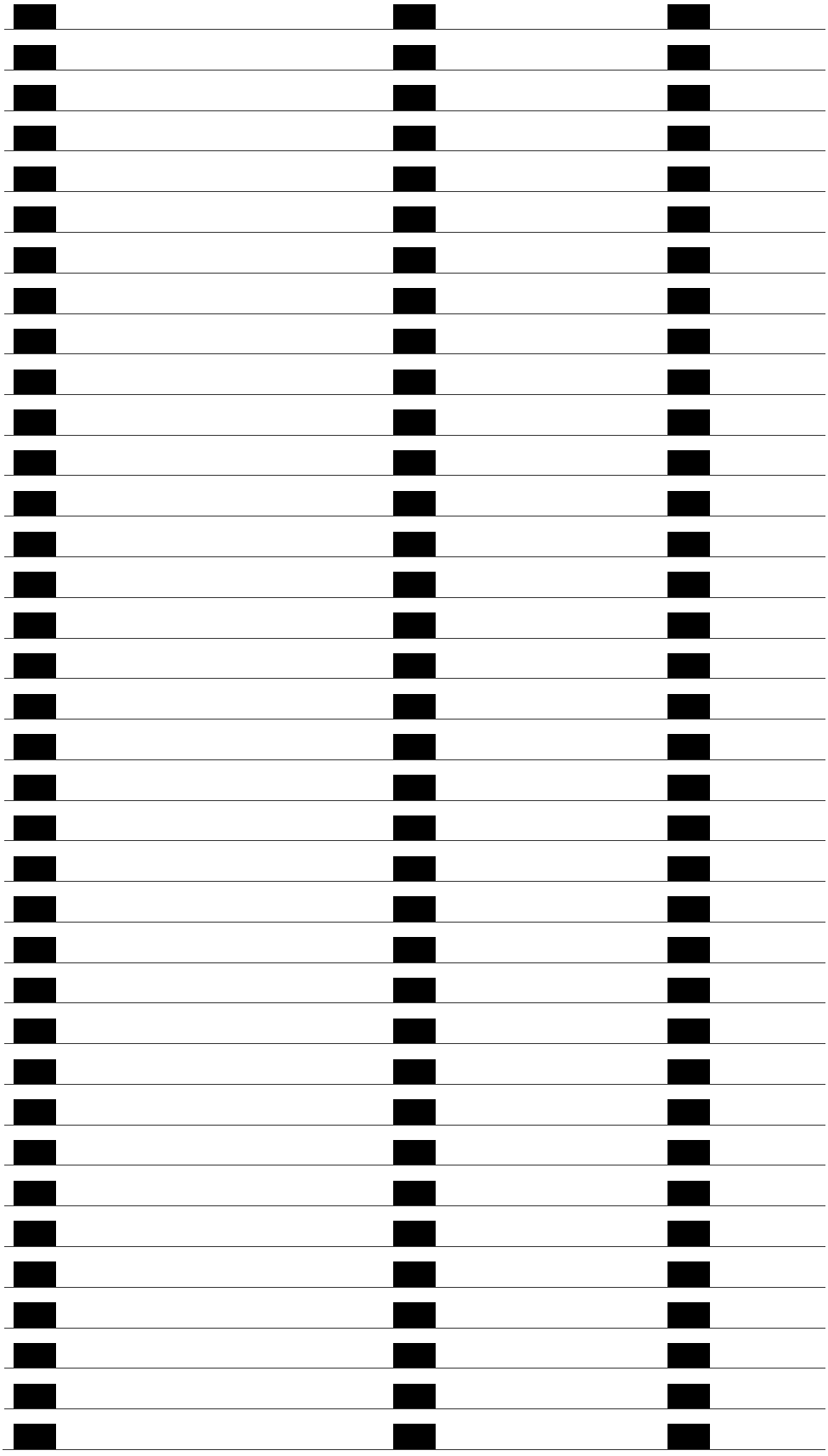
Pseudomonal bacteraemia	0 (0.00%)	1 (0.21%)
Respiratory syncytial virus bronchiolitis	1 (0.10%)	2 (0.42%)
Salmonellosis	1 (0.10%)	0 (0.00%)
Sepsis	2 (0.21%)	1 (0.21%)
Sepsis neonatal	1 (0.10%)	0 (0.00%)
Staphylococcal scalded skin syndrome	0 (0.00%)	1 (0.21%)
Tonsillitis	1 (0.10%)	0 (0.00%)
Upper respiratory tract infection	3 (0.31%)	3 (0.63%)
Urinary tract infection	0 (0.00%)	4 (0.84%)
Viral upper respiratory tract infection	1 (0.10%)	0 (0.00%)
Exposure to toxic agent	1 (0.10%)	0 (0.00%)
Fall	1 (0.10%)	0 (0.00%)
Palate injury	0 (0.00%)	1 (0.21%)
Thermal burn	2 (0.21%)	0 (0.00%)
Dehydration	2 (0.21%)	1 (0.21%)
Hypoglycaemia	1 (0.10%)	0 (0.00%)
Eyelid haemangioma	1 (0.10%)	0 (0.00%)
Cerebrovascular accident	0 (0.00%)	1 (0.21%)
Febrile convulsion	1 (0.10%)	0 (0.00%)
Hypotonia	0 (0.00%)	1 (0.21%)
Infantile spasms	0 (0.00%)	1 (0.21%)
Intraventricular haemorrhage	0 (0.00%)	1 (0.21%)
Seizure	0 (0.00%)	1 (0.21%)
Irritability	0 (0.00%)	1 (0.21%)
Nephrolithiasis	2 (0.21%)	0 (0.00%)
Penile adhesion	0 (0.00%)	1 (0.21%)
Apnoea	1 (0.10%)	1 (0.21%)
Asthma	1 (0.10%)	0 (0.00%)
Laryngeal stenosis	0 (0.00%)	1 (0.21%)
Pneumonia aspiration	2 (0.21%)	0 (0.00%)
Pulmonary vein stenosis	1 (0.10%)	0 (0.00%)
Dermatitis allergic	0 (0.00%)	1 (0.21%)

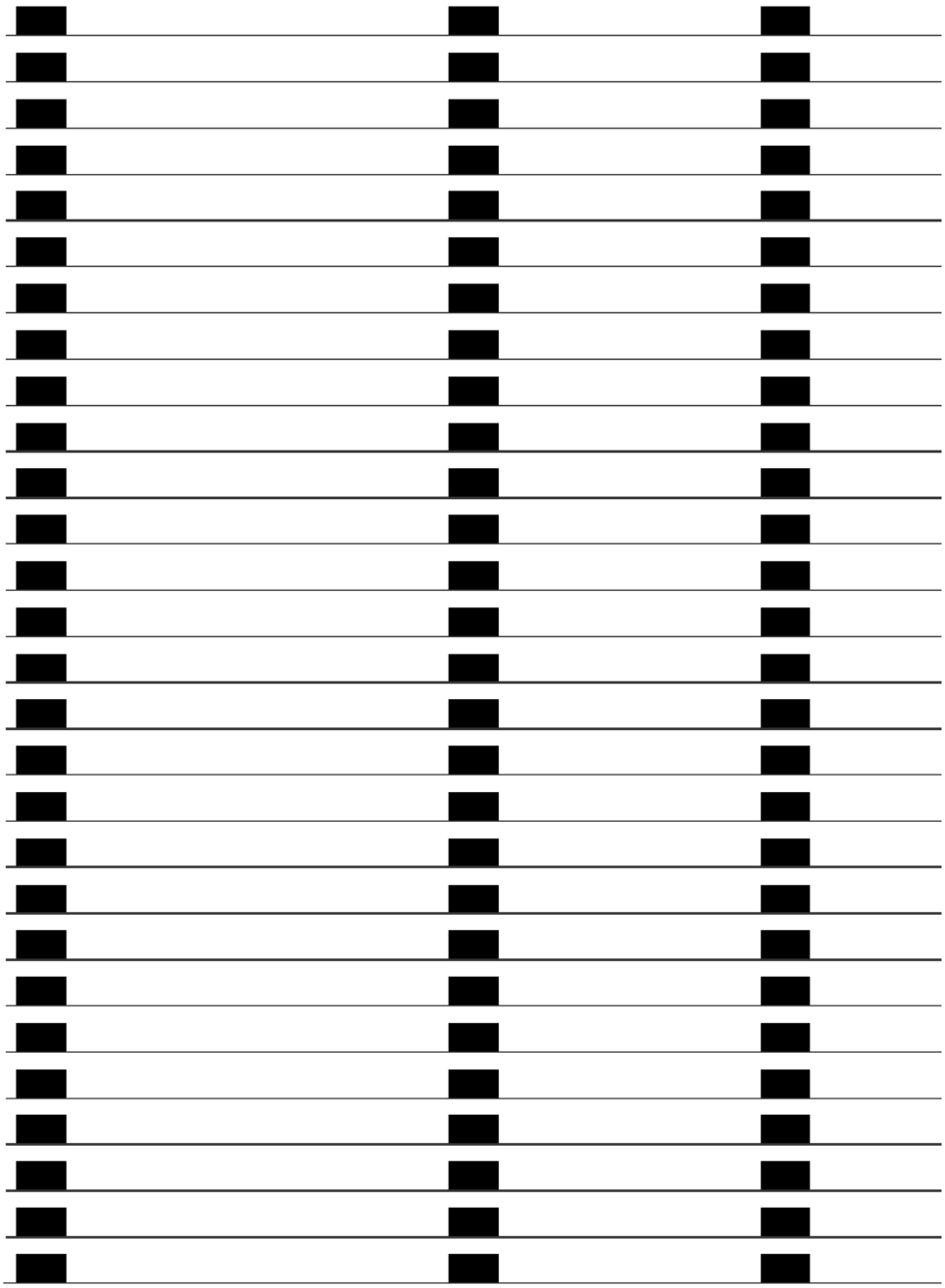
Source: clinicaltrials.gov

Notes: Infection-related AE account for all types of infections (including RSV)

Table 79. All serious adverse events observed in HARMONIE

Adverse event	Nirsevimab (n = [redacted])	Placebo (n = [redacted])
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]





Source: clinical study report[124]Source: clinical study report[124]

Notes: Infection-related AE account for all types of infections (including RSV)

Table 80. All serious adverse events observed in MEDLEY

Adverse event	Nirsevimab (n = 614)	Placebo (n = 304)
Anaemia	0 (0.00%)	1 (0.33%)
Arrhythmia	0 (0.00%)	0 (0.00%)
Atrioventricular block second degree	1 (0.16%)	0 (0.00%)

Bradycardia	1 (0.16%)	2 (0.66%)
Cardiac failure	1 (0.16%)	2 (0.66%)
Cardiac failure congestive	1 (0.16%)	1 (0.33%)
Cardiogenic shock	1 (0.16%)	1 (0.33%)
Tricuspid valve incompetence	1 (0.16%)	0 (0.00%)
Atrial septal defect	0 (0.00%)	1 (0.33%)
Atrioventricular septal defect	0 (0.00%)	1 (0.33%)
Craniosynostosis	0 (0.00%)	1 (0.33%)
Fallot's tetralogy	1 (0.16%)	0 (0.00%)
Vascular malformation	0 (0.00%)	1 (0.33%)
Ventricular septal defect	1 (0.16%)	1 (0.33%)
Retinopathy of prematurity	1 (0.16%)	0 (0.00%)
Diarrhoea	0 (0.00%)	1 (0.33%)
Duodenal ulcer	0 (0.00%)	0 (0.00%)
Enterocolitis	1 (0.16%)	0 (0.00%)
Gastric fistula	1 (0.16%)	0 (0.00%)
Incarcerated inguinal hernia	1 (0.16%)	0 (0.00%)
Inguinal hernia	1 (0.16%)	1 (0.33%)
Intestinal obstruction	0 (0.00%)	0 (0.00%)
Intussusception	1 (0.16%)	0 (0.00%)
Vomiting	0 (0.00%)	1 (0.33%)
Abdominal distension	0 (0.00%)	1 (0.33%)
Anal fissure	1 (0.16%)	0 (0.00%)
Ascites	1 (0.16%)	0 (0.00%)
Crying	0 (0.00%)	1 (0.33%)
Fatigue	1 (0.16%)	0 (0.00%)
Hyperthermia	1 (0.16%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	1 (0.33%)
Pyrexia	2 (0.33%)	0 (0.00%)
Systemic inflammatory response syndrome	1 (0.16%)	0 (0.00%)
Adenovirus infection	1 (0.16%)	0 (0.00%)
Bacterial infection	1 (0.16%)	1 (0.33%)
Bone abscess	0 (0.00%)	0 (0.00%)
Bronchiolitis	11 (1.79%)	4 (1.32%)
Bronchitis	5 (0.81%)	2 (0.66%)

Bronchitis viral	0 (0.00%)	0 (0.00%)
Covid-19	3 (0.49%)	1 (0.33%)
Dacryocystitis	1 (0.16%)	0 (0.00%)
Ear infection	0 (0.00%)	0 (0.00%)
Gastric infection	1 (0.16%)	0 (0.00%)
Gastroenteritis	6 (0.98%)	1 (0.33%)
Gastroenteritis norovirus	0 (0.00%)	1 (0.33%)
Gastroenteritis viral	1 (0.16%)	0 (0.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)
Gastrointestinal viral infection	1 (0.16%)	0 (0.00%)
Hand-foot-and-mouth disease	1 (0.16%)	0 (0.00%)
Lower respiratory tract infection	1 (0.16%)	2 (0.66%)
Lower respiratory tract infection viral	2 (0.33%)	0 (0.00%)
Mastoiditis	0 (0.00%)	0 (0.00%)
Meningitis aseptic	0 (0.00%)	0 (0.00%)
Metapneumovirus bronchiolitis	1 (0.16%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	1 (0.33%)
Otitis media	0 (0.00%)	0 (0.00%)
Otitis media acute	0 (0.00%)	0 (0.00%)
Pharyngitis	0 (0.00%)	1 (0.33%)
Pneumonia	5 (0.81%)	1 (0.33%)
Pneumonia respiratory syncytial viral	1 (0.16%)	0 (0.00%)
Pneumonia viral	1 (0.16%)	1 (0.33%)
Pyelonephritis	1 (0.16%)	0 (0.00%)
Pyelonephritis acute	1 (0.16%)	1 (0.33%)
Respiratory syncytial virus bronchiolitis	4 (0.65%)	2 (0.66%)
Rotavirus infection	0 (0.00%)	0 (0.00%)
Scrotal infection	1 (0.16%)	0 (0.00%)
Sepsis	2 (0.33%)	1 (0.33%)
Septic shock	1 (0.16%)	0 (0.00%)
Upper respiratory tract infection	1 (0.16%)	4 (1.32%)

Urinary tract infection	2 (0.33%)	1 (0.33%)
Varicella	1 (0.16%)	0 (0.00%)
Viral infection	1 (0.16%)	0 (0.00%)
Viral upper respiratory tract infection	3 (0.49%)	1 (0.33%)
Endotracheal intubation complication	0 (0.00%)	1 (0.33%)
Gastrostomy tube site complication	1 (0.16%)	0 (0.00%)
Head injury	1 (0.16%)	0 (0.00%)
Lower limb fracture	0 (0.00%)	1 (0.33%)
Skull fracture	1 (0.16%)	0 (0.00%)
Vaccination complication	0 (0.00%)	1 (0.33%)
Catheterisation cardiac	0 (0.00%)	0 (0.00%)
Oxygen saturation decreased	0 (0.00%)	1 (0.33%)
Dehydration	1 (0.16%)	0 (0.00%)
Failure to thrive	2 (0.33%)	0 (0.00%)
Feeding disorder	1 (0.16%)	0 (0.00%)
Feeding intolerance	2 (0.33%)	0 (0.00%)
Hypophagia	1 (0.16%)	0 (0.00%)
Underweight	0 (0.00%)	1 (0.33%)
Haemangioma	1 (0.16%)	0 (0.00%)
Dyskinesia	1 (0.16%)	0 (0.00%)
Embolic stroke	1 (0.16%)	0 (0.00%)
Epilepsy	0 (0.00%)	1 (0.33%)
Haemorrhage intracranial	1 (0.16%)	0 (0.00%)
Hypotonia	1 (0.16%)	0 (0.00%)
Loss of consciousness	1 (0.16%)	0 (0.00%)
Nystagmus	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)
Calculus urinary	1 (0.16%)	0 (0.00%)
Hydronephrosis	1 (0.16%)	0 (0.00%)
Intermenstrual bleeding	1 (0.16%)	0 (0.00%)
Anaemic hypoxia	0 (0.00%)	1 (0.33%)
Apnoea	0 (0.00%)	1 (0.33%)
Bronchopulmonary dysplasia	1 (0.16%)	0 (0.00%)
Chylothorax	0 (0.00%)	1 (0.33%)

Diaphragm muscle weakness	0 (0.00%)	1 (0.33%)
Hypoxia	1 (0.16%)	0 (0.00%)
Infantile apnoea	1 (0.16%)	0 (0.00%)
Laryngeal stenosis	0 (0.00%)	1 (0.33%)
Pleural effusion	0 (0.00%)	0 (0.00%)
Pulmonary artery stenosis	1 (0.16%)	0 (0.00%)
Pulmonary hypertensive crisis	1 (0.16%)	0 (0.00%)
Pulmonary oedema	0 (0.00%)	1 (0.33%)
Respiratory distress	1 (0.16%)	0 (0.00%)
Angioedema	1 (0.16%)	0 (0.00%)
Social problem	1 (0.16%)	0 (0.00%)
Social stay hospitalisation	1 (0.16%)	0 (0.00%)
Cyanosis	0 (0.00%)	0 (0.00%)

Source: Clinicaltrials.gov

Notes: Infection-related AE account for all types of infections (including RSV)

Table 81. All serious adverse events observed in Simoes et al. 2022

Adverse event	Abrysvo, 120ug, no adjuvant (n = 79)	Abrysvo, 120ug, adjuvant (n = 84)	Abrysvo, 240ug, no adjuvant (n = 77)	Abrysvo, 240ug, adjuvant (n = 85)	Placebo (n = 78)
Cyanosis	0	1 (1.2%)	0	0	0
Mitral valve incompetence	1 (1.3%)	0	0	0	0
Ankyloglossia congenital	3 (3.8%)	0	2 (2.6%)	2 (2.4%)	2 (2.6%)
Aplasia cutis congenita	0	0	0	0	1 (1.3%)
Atrial septal defect	1 (1.3%)	2 (2.4%)	0	0	0
Birth mark	1 (1.3%)	0	0	0	0
Chordee	1 (1.3%)	0	1 (1.3%)	0	0
Cleft lip	1 (1.3%)	0	0	0	0
Congenital naevus	5 (6.3%)	3 (3.6%)	4 (5.2%)	4 (4.7%)	0
Congenital skin dimples	0	0	1 (1.3%)	0	0
Cryptorchism	0	0	0	2 (2.4%)	1 (1.3%)
Cystic fibrosis	0	0	0	0	1 (1.3%)
Dacryostenosis congenital	1 (1.3%)	0	1 (1.3%)	0	1 (1.3%)

Gastrointestinal disorder congenital	1 (1.3%)	0	0	0	0
Hydrocele	1 (1.3%)	0	0	1 (1.2%)	1 (1.3%)
Hypospadias	0	1 (1.2%)	0	0	0
Labial tie	1 (1.3%)	0	0	0	1 (1.3%)
Laryngomalacia	0	1 (1.2%)	0	0	0
Naevus flammeus	1 (1.3%)	1 (1.2%)	2 (2.6%)	1 (1.2%)	0
Patent ductus arteriosus	1 (1.3%)	0	0	0	0
Penile torsion	0	0	0	1 (1.2%)	0
Penoscrotal fusion	0	0	1 (1.3%)	0	1 (1.3%)
Spina bifida cystica	0	1 (1.2%)	0	0	0
XYY syndrome	0	0	0	0	1 (1.3%)
Tongue cyst	1 (1.3%)	0	0	0	0
Umbilical hernia	2 (2.5%)	3 (3.6%)	4 (5.2%)	3 (3.5%)	1 (1.3%)
Pyrexia	0	1 (1.2%)	0	0	0
Swelling	0	1 (1.2%)	0	0	0
Hyperbilirubinaemia	0	1 (1.2%)	0	0	1 (1.3%)
Jaundice	1 (1.3%)	3 (3.6%)	1 (1.3%)	3 (3.5%)	0
Bronchiolitis	0	0	0	0	1 (1.3%)
Gastroenteritis viral	0	0	1 (1.3%)	0	0
Respiratory syncytial virus infection	0	0	0	0	2 (2.6%)
Sepsis	0	0	1 (1.3%)	0	0
Urinary tract infection	0	0	0	1 (1.2%)	0
Cardiac murmur	0	0	0	1 (1.2%)	0
Cardiac murmur functional	0	1 (1.2%)	0	0	0
Right ventricular systolic pressure	0	1 (1.2%)	0	0	0
Metabolic acidosis	0	1 (1.2%)	0	0	0
Underweight	0	1 (1.2%)	0	0	0
Seizure	0	1 (1.2%)	1 (1.3%)	0	0
Low birth weight baby	0	0	0	1 (1.2%)	0
Premature baby	2 (2.5%)	2 (2.4%)	1 (1.3%)	1 (1.2%)	1 (1.3%)

Acute respiratory failure	0	1 (1.2%)	0	0	0
Meconium aspiration syndrome	0	2 (2.4%)	0	0	0
Neonatal aspiration	0	1 (1.2%)	0	0	0
Neonatal respiratory depression	0	0	0	1 (1.2%)	0
Neonatal respiratory failure	0	1 (1.2%)	0	0	0
Pneumothorax	0	0	0	1 (1.2%)	1 (1.3%)
Respiratory depression	0	0	0	0	1 (1.3%)
Respiratory distress	0	0	0	2 (2.4%)	1 (1.3%)

Source: Simoes et al. 2022[109]2022[109]

Notes: Infection-related AE account for all types of infections (including RSV)

Table 82. All serious adverse events observed in MATISSE

Adverse event	Abrysvo (n = 3568)	Placebo (n = 3558)
Pulmonary valve stenosis	6 (0.2%)	6 (0.2%)
Ankyloglossia congenital	15 (0.4%)	10 (0.3%)
Atrial septal defect	31 (0.9%)	40 (1.1%)
Cryptochism	7 (0.2%)	16 (0.4%)
Developmental hip dysplasia	11 (0.3%)	12 (0.3%)
Hypospadias	7 (0.2%)	11 (0.3%)
Microcephaly	5 (0.1%)	7 (0.2%)
Patent ductus arteriosus	12 (0.3%)	10 (0.3%)
Ventricular septal defect	15.(0.4%)	20 (0.6%)
Inguinal hernia	6 (0.2%)	6 (0.2%)
Pyrexia	2 (<0.1%)	6 (0.2%)
Hyperbilirubinemia neonatal	49 (1.4%)	40 (1.1%)
Gastroenteritis	14 (0.4%)	12 (0.3%)
Infection	13 (0.4%)	12 (0.3%)
Sepsis	9 (0.3%)	4 (0.1%)
Sepsis neonatal	19 (0.5%)	19 (0.5%)
Urinary tract infection	12 (0.3%)	14 (0.4%)
Dehydration	6 (0.2%)	8 (0.2%)
Failure to thrive	6 (0.2%)	5 (0.1%)

Hypoglycemia	20 (0.6%)	17 (0.5%)
Hypoglycemia neonatal	13 (0.4%)	10 (0.3%)
Torticollis	5 (0.1%)	7 (0.2%)
Cerebral cyst	6 (0.2%)	3 (<0.1%)
Febrile convulsion	5 (0.1%)	6 (0.2%)
Hypoxic-ischemic encephalopathy	6 (0.2%)	3 (<0.1%)
Jaundice neonatal	75 (2.1%)	66 (1.9%)
Low birth weight baby	27 (0.8%)	31 (0.9%)
Premature baby	49 (1.4%)	42 (1.2%)
Small for dates baby	6 (0.2%)	10 (0.3%)
Hydronephrosis	5 (0.1%)	9 (0.3%)
Pyelocaliectasis	5 (0.1%)	8 (0.2%)
Hypoxia	6 (0.2%)	3 (<0.1%)
Infantile apnea	10 (0.3%)	3 (<0.1%)
Meconium aspiration syndrome	9 (0.3%)	7 (0.2%)
Neonatal asphyxia	8 (0.2%)	7 (0.2%)
Neonatal respiratory distress	11 (0.3%)	14 (0.4%)
Neonatal respiratory distress syndrome	10 (0.3%)	14 (0.4%)
Respiratory distress	47 (1.3%)	43 (1.2%)
Tachypnea	6 (0.2%)	8 (0.2%)
Transient tachypnea of the newborn	33 (0.9%)	29 (0.8%)

Source: Kampmann et al. 2023[79]

Notes: Infection-related AE account for all types of infections (including RSV)

Appendix F. Health-related quality of life

No HRQoL instrument has been utilized in the analysis. There is an overall scarcity of RSV-associated health-related quality of life data for both infants and caregivers. The QALY-relevant inputs for the cost-effectiveness model were selected based on AE-related utility decrements available in the literature at the time the cost-effectiveness analysis was conducted. Therefore, this appendix is not relevant for this submission.

Appendix G. Probabilistic sensitivity analyses

Table 83 and Table 84 show which data/assumptions (point estimate, and lower and upper bound) form the basis for the selected probability distributions used in the probabilistic analysis. The PSA simultaneously varied all parameters with uncertainty in the model, sampling various input parameters from the appropriate probability distributions.

A ±20% variation from the base-case parameter value was assumed to determine the lower-bound and upper-bound values.

Correlation within a group of parameters such as the % of RSV infections by month that needs to add up to 100%, is handled through the use of the Dirichlet distribution that maintains this relationship during the PSA run.

Table 83. Overview of parameters in the PSA (Model 1)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Clinical				
Variance of distribution of births by month – January	0.082	0.066	0.099	Dirichlet
Variance of distribution of births by month – February	0.077	0.060	0.094	Dirichlet
Variance of distribution of births by month – March	0.084	0.067	0.101	Dirichlet
Variance of distribution of births by month – April	0.079	0.062	0.096	Dirichlet
Variance of distribution of births by month – May	0.085	0.068	0.102	Dirichlet

Variance of distribution of births by month – June	0.087	0.070	0.103	Dirichlet
Variance of distribution of births by month – July	0.091	0.074	0.108	Dirichlet
Variance of distribution of births by month - August	0.089	0.072	0.106	Dirichlet
Variance of distribution of births by month – September	0.086	0.069	0.102	Dirichlet
Variance of distribution of births by month – October	0.087	0.070	0.103	Dirichlet
Variance of distribution of births by month - November	0.077	0.060	0.094	Dirichlet
Variance of distribution of births by month - December	0.077	0.060	0.094	Dirichlet
% of RSV infection by month – January	0.173	0.1384	0.2076	Dirichlet
% of RSV infection by month – February	0.058	0.0464	0.0696	Dirichlet
% of RSV infection by month – March	0.026	0.0208	0.0312	Dirichlet
% of RSV infection by month - April	0.007	0.0056	0.0084	Dirichlet

% of RSV infection by month – May	0.002	0.0016	0.0024	Dirichlet
% of RSV infection by month - June	0.001	0.0008	0.0012	Dirichlet
% of RSV infection by month – July	0.000	0.0	0.0	Dirichlet
% of RSV infection by month - August	0.001	0.0008	0.0012	Dirichlet
% of RSV infection by month - September	0.007	0.0056	0.0084	Dirichlet
% of RSV infection by month - October	0.026	0.0208	0.0312	Dirichlet
% of RSV infection by month – November	0.193	0.1544	0.2316	Dirichlet
% of RSV infection by month - December	0.505	0.404	0.606	Dirichlet
End of protection: nirsevimab	5	4	6	Normal
End of protection: maternal immunisation	6	4.8	7.2	Normal
Efficacy nirsevimab 1st dose (inpatient) – palivizumab eligible population	0.560	0.448	0.672	Log-normal
Efficacy nirsevimab 1st dose (inpatient) – preterm infant population	0.802	0.6416	0.9624	Log-normal

Efficacy nirsevimab 1st dose (inpatient) – term infant population	0.802	0.6416	0.9624	Log-normal
Efficacy maternal immunisation (inpatient) - palivizumab eligible population	0.000	0.000	0.000	Log-normal
Efficacy maternal immunisation (inpatient) – preterm infant population	0.566	0.4528	0.6792	Log-normal
Efficacy maternal immunisation (inpatient) – term infant population	0.566	0.4528	0.6792	Log-normal
Efficacy nirsevimab 1st dose (outpatient) - palivizumab eligible population	0.560	0.448	0.672	Log-normal
Efficacy nirsevimab 1st dose (outpatient) – preterm infant population	0.802	0.6416	0.9624	Log-normal
Efficacy nirsevimab 1st dose (outpatient) – term infant population	0.802	0.6416	0.9624	Log-normal
Efficacy maternal immunisation (outpatient) - palivizumab eligible population	0.000	0.000	0.000	Log-normal

Efficacy maternal immunisation (outpatient) – preterm infant population	0.566	0.4528	0.6792	Log-normal
Efficacy maternal immunisation (outpatient) – term infant population	0.566	0.4528	0.6792	Log-normal
RSV risk by age (palivizumab eligible population)				
RSV risk by age – inpatient hospitalisation – 0 months	0.209586908	0.1676695264	0.2515042896	Beta
RSV risk by age inpatient hospitalisation – 1 months	0.512748536	0.4101988288	0.6152982432	Beta
RSV risk by age inpatient hospitalisation – 2 months	0.438085835	0.350468668	0.525702702	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.25993413	0.207947304	0.311920956	Beta
RSV risk by age inpatient hospitalisation – 4 months	0.17807487	0.142459896	0.213689844	Beta
RSV risk by age inpatient hospitalisation – 5 months	0.148637891	0.1189103128	0.1783654692	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.077479097	0.0619832776	0.0929749164	Beta
RSV risk by age inpatient	0.066991912	0.0535935296	0.0803902944	Beta

hospitalisation – 7 months				
RSV risk by age inpatient hospitalisation – 8 months	0.056879983	0.0455039864	0.0682559796	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.046893003	0.0375144024	0.0562716036	Beta
RSV risk by age inpatient hospitalisation – 10 months	0.032663757	0.0261310056	0.0391965084	Beta
RSV risk by age inpatient hospitalisation – 11 months	0.049801015	0.039840812	0.059761218	Beta
RSV risk by age – ICU – 0 months	0.054733063	0.04378645	0.065679676	Beta
RSV risk by age ICU – 1 months	0.089588241	0.071670593	0.107505889	Beta
RSV risk by age ICU – 2 months	0.052340965	0.041872772	0.062809158	Beta
RSV risk by age ICU – 3 months	0.018119481	0.014495585	0.021743377	Beta
RSV risk by age ICU – 4 months	0.01092834	0.008742672	0.013114008	Beta
RSV risk by age ICU – 5 months	0.009616369	0.007693095	0.011539643	Beta
RSV risk by age ICU – 6 months	0.005098408	0.004078726	0.00611809	Beta
RSV risk by age ICU – 7 months	0.004599402	0.003679522	0.005519282	Beta
RSV risk by age ICU – 8 months	0.004157479	0.003325983	0.004988975	Beta

RSV risk by age ICU – 9 months	0.004002338	0.00320187	0.004802806	Beta
RSV risk by age ICU – 10 months	0.002486189	0.001988951	0.002983427	Beta
RSV risk by age ICU – 11 months	0.004205399	0.003364319	0.005046479	Beta
RSV risk by age – MV – 0 months	0.008755362	0.007	0.011	Beta
RSV risk by age MV – 1 months	0.019716576	0.018	0.021	Beta
RSV risk by age MV – 2 months	0.015696141	0.014	0.017	Beta
RSV risk by age MV – 3 months	0.003390944	0.002	0.005	Beta
RSV risk by age MV – 4 months	0.002289605	0.001	0.004	Beta
RSV risk by age MV – 5 months	0.001912435	0.000	0.004	Beta
RSV risk by age MV – 6 months	0.002252151	0.001	0.004	Beta
RSV risk by age MV – 7 months	0.001969839	0.000	0.004	Beta
RSV risk by age MV – 8 months	0.001676425	0.000	0.003	Beta
RSV risk by age MV – 9 months	0.001330672	0.000	0.003	Beta
RSV risk by age MV – 10 months	0.000951613	-0.001	0.003	Beta
RSV risk by age MV – 11 months	0.001505135	0.000	0.003	Beta
RSV risk by age – outpatient	0	0	0	Beta

hospitalisation – 0 months				
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 4 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 7 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta
RSV risk by age outpatient	0	0	0	Beta

hospitalisation – 10 months				
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta
RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta
RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta
RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta
RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta

RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta
RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta
RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta
RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta
RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta
RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta

RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age (preterm infant population)				
RSV risk by age – inpatient hospitalisation – 0 months	0.048008746	0.038406997	0.057610495	Beta
RSV risk by age inpatient	0.121051239	0.096840991	0.145261487	Beta

hospitalisation – 1 months				
RSV risk by age inpatient hospitalisation – 2 months	0.106016015	0.084812812	0.127219218	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.065381574	0.052305259	0.078457889	Beta
RSV risk by age inpatient hospitalisation – 4 months	0.044833109	0.035866487	0.053799731	Beta
RSV risk by age inpatient hospitalisation – 5 months	0.037449802	0.029959842	0.044939762	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.019586394	0.015669115	0.023503673	Beta
RSV risk by age inpatient hospitalisation – 7 months	0.016937811	0.013550249	0.020325373	Beta
RSV risk by age inpatient hospitalisation – 8 months	0.014384521	0.011507617	0.017261425	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.01186651	0.009493208	0.014239812	Beta
RSV risk by age inpatient hospitalisation – 10 months	0.008261728	0.006609382	0.009914074	Beta
RSV risk by age inpatient	0.012601799	0.010081439	0.015122159	Beta

hospitalisation – 11 months				
RSV risk by age – ICU – 0 months	0.017097786	0.013678229	0.020517343	Beta
RSV risk by age ICU – 1 months	0.027986019	0.022388815	0.033583223	Beta
RSV risk by age ICU – 2 months	0.01635053	0.013080424	0.019620636	Beta
RSV risk by age ICU – 3 months	0.004249912	0.00339993	0.005099894	Beta
RSV risk by age ICU – 4 months	0.002563235	0.002050588	0.003075882	Beta
RSV risk by age ICU – 5 months	0.002255513	0.00180441	0.002706616	Beta
RSV risk by age ICU – 6 months	0.001216808	0.000973446	0.00146017	Beta
RSV risk by age ICU – 7 months	0.001097713	0.00087817	0.001317256	Beta
RSV risk by age ICU – 8 months	0.000992242	0.000793794	0.00119069	Beta
RSV risk by age ICU – 9 months	0.000955215	0.000764172	0.001146258	Beta
RSV risk by age ICU – 10 months	0.000593364	0.000474691	0.000712037	Beta
RSV risk by age ICU – 11 months	0.001003678	0.000802942	0.001204414	Beta
RSV risk by age – MV – 0 months	0.005680392	0.004544314	0.00681647	Beta
RSV risk by age MV – 1 months	0.01037086	0.008296688	0.012445032	Beta
RSV risk by age MV – 2 months	0.004536438	0.00362915	0.005443726	Beta

RSV risk by age MV – 3 months	0.002500267	0.002000214	0.00300032	Beta
RSV risk by age MV – 4 months	0.001307872	0.001046298	0.001569446	Beta
RSV risk by age MV – 5 months	0.000975771	0.000780617	0.001170925	Beta
RSV risk by age MV – 6 months	0.000897453	0.000717962	0.001076944	Beta
RSV risk by age MV – 7 months	0.000944908	0.000755926	0.00113389	Beta
RSV risk by age MV – 8 months	0.000776472	0.000621178	0.000931766	Beta
RSV risk by age MV – 9 months	0	0	0	Beta
RSV risk by age MV – 10 months	0.000314199	0.000251359	0.000377039	Beta
RSV risk by age MV – 11 months	0.000897284	0.000717827	0.001076741	Beta
RSV risk by age – outpatient hospitalisation – 0 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta
RSV risk by age outpatient	0	0	0	Beta

hospitalisation – 4 months				
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 7 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 10 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta
RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta

RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta
RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta
RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta
RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta
RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta

RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta
RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta
RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta
RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta
RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta

RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age (term infant population)				
RSV risk by age – inpatient hospitalisation – 0 months	0.033909973	0.027127978	0.040691968	Beta
RSV risk by age inpatient hospitalisation – 1 months	0.079869844	0.063895875	0.095843813	Beta
RSV risk by age inpatient hospitalisation – 2 months	0.066080835	0.052864668	0.079297002	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.038239608	0.030591686	0.04588753	Beta
RSV risk by age inpatient	0.026038924	0.020831139	0.031246709	Beta

hospitalisation – 4 months				
RSV risk by age inpatient hospitalisation – 5 months	0.021716335	0.017373068	0.026059602	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.011409196	0.009127357	0.013691035	Beta
RSV risk by age inpatient hospitalisation – 7 months	0.009925037	0.00794003	0.011910044	Beta
RSV risk by age inpatient hospitalisation – 8 months	0.008421958	0.006737566	0.01010635	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.006734829	0.005387863	0.008081795	Beta
RSV risk by age inpatient hospitalisation – 10 months	0.004793205	0.003834564	0.005751846	Beta
RSV risk by age inpatient hospitalisation – 11 months	0.007455996	0.005964797	0.008947195	Beta
RSV risk by age – ICU – 0 months	0.004830316	0.003864253	0.005796379	Beta
RSV risk by age ICU – 1 months	0.007906364	0.006325091	0.009487637	Beta
RSV risk by age ICU – 2 months	0.004619208	0.003695366	0.00554305	Beta
RSV risk by age ICU – 3 months	0.002045548	0.001636438	0.002454658	Beta

RSV risk by age ICU – 4 months	0.001233724	0.000986979	0.001480469	Beta
RSV risk by age ICU – 5 months	0.001085613	0.00086849	0.001302736	Beta
RSV risk by age ICU – 6 months	0.000649328	0.000519462	0.000779194	Beta
RSV risk by age ICU – 7 months	0.000585775	0.00046862	0.00070293	Beta
RSV risk by age ICU – 8 months	0.000529492	0.000423594	0.00063539	Beta
RSV risk by age ICU – 9 months	0.000509733	0.000407786	0.00061168	Beta
RSV risk by age ICU – 10 months	0.000316638	0.00025331	0.000379966	Beta
RSV risk by age ICU – 11 months	0.000535595	0.000428476	0.000642714	Beta
RSV risk by age – MV – 0 months	0.00125591	0.001004728	0.001507092	Beta
RSV risk by age MV – 1 months	0.002292953	0.001834362	0.002751544	Beta
RSV risk by age MV – 2 months	0.001002987	0.00080239	0.001203584	Beta
RSV risk by age MV – 3 months	0.000470902	0.000376722	0.000565082	Beta
RSV risk by age MV – 4 months	0.000246326	0.000197061	0.000295591	Beta
RSV risk by age MV – 5 months	0.000183778	0.000147022	0.000220534	Beta
RSV risk by age MV – 6 months	0.000202832	0.000162266	0.000243398	Beta
RSV risk by age MV – 7 months	0.000213558	0.000170846	0.00025627	Beta

RSV risk by age MV – 8 months	0.00017549	0.000140392	0.000210588	Beta
RSV risk by age MV – 9 months	0	0	0	Beta
RSV risk by age MV – 10 months	7.10117E-05	5.68094E-05	8.5214E-05	Beta
RSV risk by age MV – 11 months	0.000202794	0.000162235	0.000243353	Beta
RSV risk by age – outpatient hospitalisation – 0 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 4 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta
RSV risk by age outpatient	0	0	0	Beta

hospitalisation – 7 months				
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 10 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta
RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta
RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta
RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta

RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta
RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta
RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta
RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta
RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta

RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta
RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta
RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta

RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
Coverage rate palivizumab eligible population				
Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal

Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of maternal immunisation – January	0	0	0	Normal
Coverage rate of maternal immunisation – February	0	0	0	Normal
Coverage rate of maternal immunisation – March	0	0	0	Normal
Coverage rate of maternal immunisation – April	0	0	0	Normal
Coverage rate of maternal immunisation – May	0	0	0	Normal
Coverage rate of maternal immunisation – June	0	0	0	Normal
Coverage rate of maternal immunisation – July	0	0	0	Normal
Coverage rate of maternal immunisation – August	0	0	0	Normal
Coverage rate of maternal	0	0	0	Normal

immunisation – September				
Coverage rate of maternal immunisation – October	0	0	0	Normal
Coverage rate of maternal immunisation – November	0	0	0	Normal
Coverage rate of maternal immunisation – December	0	0	0	Normal
Coverage rate preterm infant population				
Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal

Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of maternal immunisation – January	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – February	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – March	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – April	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – May	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – June	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – July	0.21503268	0.172026144	0.258039216	Normal

Coverage rate of maternal immunisation – August	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – September	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – October	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – November	0.21503268	0.172026144	0.258039216	Normal
Coverage rate of maternal immunisation – December	0.21503268	0.172026144	0.258039216	Normal
Coverage rate term infant population				
Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal

Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of maternal immunisation – January	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – February	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – March	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – April	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – May	0.7	0.56	0.84	Normal
Coverage rate of maternal	0.7	0.56	0.84	Normal

immunisation – June				
Coverage rate of maternal immunisation – July	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – August	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – September	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – October	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – November	0.7	0.56	0.84	Normal
Coverage rate of maternal immunisation – December	0.7	0.56	0.84	Normal
RSV complication risk				
Risk of complication – Recurrent wheezing: palivizumab eligible population	0.31	0.248	0.372	Beta
Risk of complication Recurrent wheezing: preterm infant population	0.31	0.248	0.372	Beta

Risk of complication Recurrent wheezing: term infant population	0.31	0.248	0.372	Beta
Risk of complication – Asthma: palivizumab eligible population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication Asthma: preterm infant population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication Asthma: term infant population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication – Excess HCRU: palivizumab eligible population	0.1	0.08	0.12	Beta
Risk of complication Excess HCRU: preterm infant population	0.1	0.08	0.12	Beta
Risk of complication Excess HCRU: term infant population	0.1	0.08	0.12	Beta
Risk of complication – Otis Media: palivizumab eligible population	0.1	0.08	0.12	Beta
Risk of complication Otis	0.1	0.08	0.12	Beta

Media: preterm infant population				
Risk of complication Otis Media: term infant population	0.1	0.08	0.12	Beta
Risk of complication – Recurrent wheezing /year 2: palivizumab eligible population	0.27	0.216	0.324	Beta
Risk of complication Recurrent wheezing /year 2: preterm infant population	0.27	0.216	0.324	Beta
Risk of complication Recurrent wheezing /year 2: term infant population	0.27	0.216	0.324	Beta
Risk of complication – Recurrent wheezing /year 3: palivizumab eligible population	0.17	0.136	0.204	Beta
Risk of complication Recurrent wheezing /year 3: preterm infant population	0.17	0.136	0.204	Beta
Risk of complication Recurrent wheezing /year 3: term infant population	0.17	0.136	0.204	Beta

RSV mortality risk				
RSV mortality risk (per case): palivizumab eligible population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): palivizumab eligible population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): palivizumab eligible population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): term infant population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): term infant population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta

RSV mortality risk (per case): term infant population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta
Disutilities				
Disutility associated with RSV event				
Hospitalizations (incl. ICU admission and MV)	0.01014	0.008112	0.012168	Beta
Intensive care or observation: Conditional on Initial Hospitalization	0.01014	0.008112	0.012168	Beta
Mechanical ventilation: Conditional on Initial Hospitalization	0.01014	0.008112	0.012168	Beta
Pediatric emergency admission (akut børnemodtagelse)	0.00630	0.00504	0.00756	Beta
Primary care visits	0.00630	0.00504	0.00756	Beta
Open hospitalisation "åben indlæggelse"	0.00382	0.003056	0.004584	Beta
All-cause LRTI hospitalizations (excl. RSV)	0.00382	0.003056	0.004584	Beta
Parent/caregiver QALY loss	0.00074	0.000592	0.000888	Beta
Costs				
RSV treatment cost: Palivizumab eligible population				

Hospitalizations Alone	219171	175336.8	263005.2	Gamma
Intensive care or observation: Conditional on Initial Hospitalization	245958	196766.4	295149.6	Gamma
Mechanical ventilation (incl. hospitalization and ICU)	435033	348026.4	522039.6	Gamma
Pediatric emergency admission (akut børnemodtagelse)	3321	2656.8	3985.2	Gamma
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation "åben indlæggelse"	3321	2656.8	3985.2	Gamma
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV treatment cost: Preterm infant population				
Hospitalizations Alone	126168	100934.4	151401.6	Gamma
Intensive care or observation: Conditional on Initial Hospitalization	160154.5	128123.6	192185.4	Gamma
Mechanical ventilation (incl. hospitalization and ICU)	263628	210902.4	316353.6	Gamma
Pediatric emergency	3321	2656.8	3985.2	Gamma

admission (akut børnemodtagelse)				
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation "åben indlæggelse"	3321	2656.8	3985.2	Gamma
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV treatment cost: Term infant population				
Hospitalizations Alone	20868	16694.4	25041.6	Gamma
Intensive care or observation: Conditional on Initial Hospitalization	54129	43303.2	64954.8	Gamma
Mechanical ventilation (incl. hospitalization and ICU)	180448	144358.4	216537.6	Gamma
Pediatric emergency admission (akut børnemodtagelse)	3321	2656.8	3985.2	Gamma
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation "åben indlæggelse"	3321	2656.8	3985.2	Gamma
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV complication management cost: Palivizumab eligible population				

Recurrent wheezing	844.855	844.855	844.855	Gamma
Asthma	844.855	844.855	844.855	Gamma
Excess HCRU	0	0	0	Gamma
Otitis media	0	0	0	Gamma
Recurrent Wheezing (Year 2)	816.2850242	816.2850242	816.2850242	Gamma
Recurrent Wheezing (Year 3)	788.6811828	788.6811828	788.6811828	Gamma
RSV complication management cost: Preterm infant population				
Recurrent wheezing	844.855	675.884	1013.826	Gamma
Asthma	844.855	675.884	1013.826	Gamma
Excess HCRU	0	0	0	Gamma
Otitis media	0	0	0	Gamma
Recurrent Wheezing (Year 2)	816.2850242	653.0280194	979.542029	Gamma
Recurrent Wheezing (Year 3)	788.6811828	630.9449462	946.4174194	Gamma
RSV complication management cost: Term infant population				
Recurrent wheezing	844.855	844.855	844.855	Gamma
Asthma	844.855	844.855	844.855	Gamma
Excess HCRU	0	0	0	Gamma
Otitis media	0	0	0	Gamma

Recurrent Wheezing (Year 2)	816.2850242	816.2850242	816.2850242	Gamma
Recurrent Wheezing (Year 3)	788.6811828	788.6811828	788.6811828	Gamma

Abbreviations: RSV= respiratory syncytial virus, ICU= intensive care unit (refers to intensive observation and care), MV= mechanical ventilation, ER= emergency room (refers to pediatric emergency admission (akut børnemodtagelse), PC= primary care, URTI= upper respiratory tract infection, HCRU= healthcare resource use, LRTI= lower respiratory tract infection, QALY= quality-adjusted life-years

Notes: Discount rates for year 1 (is 1 because this is the current year, hence no need for discounting costs and outcomes). 3.5% is applied as discount rate for both costs and outcomes: Year 1: 1 / (1+0.035)*(1-1), Year 2: 1 / (1+0.035)^(2-1) = 0.9666, Year 3: (1+0.035)^(3-1) = 0.93333

Table 84 Overview of parameters in the PSA (Model 2)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Clinical				
Variance of distribution of births by month – January	0.082	0.066	0.099	Dirichlet
Variance of distribution of births by month – February	0.077	0.060	0.094	Dirichlet
Variance of distribution of births by month - March	0.084	0.067	0.101	Dirichlet
Variance of distribution of births by month – April	0.079	0.062	0.096	Dirichlet
Variance of distribution of births by month - May	0.085	0.068	0.102	Dirichlet
Variance of distribution of births by month – June	0.087	0.070	0.103	Dirichlet
Variance of distribution of	0.091	0.074	0.108	Dirichlet

births by month - July				
Variance of distribution of births by month - August	0.089	0.072	0.106	Dirichlet
Variance of distribution of births by month – September	0.086	0.069	0.102	Dirichlet
Variance of distribution of births by month – October	0.087	0.070	0.103	Dirichlet
Variance of distribution of births by month – November	0.077	0.060	0.094	Dirichlet
Variance of distribution of births by month - December	0.077	0.060	0.094	Dirichlet
% of RSV infection by month – January	0.173	0.1384	0.2076	Dirichlet
% of RSV infection by month – February	0.058	0.0464	0.0696	Dirichlet
% of RSV infection by month – March	0.026	0.0208	0.0312	Dirichlet
% of RSV infection by month - April	0.007	0.0056	0.0084	Dirichlet
% of RSV infection by month – May	0.002	0.0016	0.0024	Dirichlet
% of RSV infection by month - June	0.001	0.0008	0.0012	Dirichlet
% of RSV infection by month – July	0.000	0.0	0.0	Dirichlet

% of RSV infection by month - August	0.001	0.0008	0.0012	Dirichlet
% of RSV infection by month - September	0.007	0.0056	0.0084	Dirichlet
% of RSV infection by month - October	0.026	0.0208	0.0312	Dirichlet
% of RSV infection by month – November	0.193	0.1544	0.2316	Dirichlet
% of RSV infection by month - December	0.505	0.404	0.606	Dirichlet
End of protection: nirsevimab	5	4	6	Normal
End of protection: Palivizumab immunisation	1	0.8	1.2	Normal
Efficacy nirsevimab 1st dose (inpatient) – palivizumab eligible population	0.560	0.448	0.672	Log-normal
Efficacy nirsevimab 1st dose (inpatient) – preterm infant population	0.802	0.6416	0.9624	Log-normal
Efficacy nirsevimab 1st dose (inpatient) – term infant population	0.802	0.6416	0.9624	Log-normal
Efficacy Palivizumab (inpatient) - palivizumab eligible population	0.560	0.448	0.672	Log-normal

Efficacy Palivizumab (inpatient) – preterm infant population	0	0	0	Log-normal
Efficacy Palivizumab (inpatient) – term infant population	0	0	0	Log-normal
Efficacy nirsevimab 1st dose (outpatient) - palivizumab eligible population	0.560	0.448	0.672	Log-normal
Efficacy nirsevimab 1st dose (outpatient) – preterm infant population	0.802	0.6416	0.9624	Log-normal
Efficacy nirsevimab 1st dose (outpatient) – term infant population	0.802	0.6416	0.9624	Log-normal
Efficacy Palivizumab (outpatient) - palivizumab eligible population	0.560	0.448	0.672	Log-normal
Efficacy Palivizumab (outpatient) – preterm infant population	0	0	0	Log-normal
Efficacy Palivizumab (outpatient) – term infant population	0	0	0	Log-normal
RSV risk by age (palivizumab eligible population)				
RSV risk by age – inpatient	0.209586908	0.1676695264	0.2515042896	Beta

hospitalisation – 0 months				
RSV risk by age inpatient hospitalisation – 1 months	0.512748536	0.4101988288	0.6152982432	Beta
RSV risk by age inpatient hospitalisation – 2 months	0.438085835	0.350468668	0.525702702	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.25993413	0.207947304	0.311920956	Beta
RSV risk by age inpatient hospitalisation – 4 months	0.17807487	0.142459896	0.213689844	Beta
RSV risk by age inpatient hospitalisation – 5 months	0.148637891	0.1189103128	0.1783654692	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.077479097	0.0619832776	0.0929749164	Beta
RSV risk by age inpatient hospitalisation – 7 months	0.066991912	0.0535935296	0.0803902944	Beta
RSV risk by age inpatient hospitalisation – 8 months	0.056879983	0.0455039864	0.0682559796	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.046893003	0.0375144024	0.0562716036	Beta
RSV risk by age inpatient	0.032663757	0.0261310056	0.0391965084	Beta

hospitalisation – 10 months				
RSV risk by age inpatient hospitalisation – 11 months	0.049801015	0.039840812	0.059761218	Beta
RSV risk by age – ICU – 0 months	0.054733063	0.04378645	0.065679676	Beta
RSV risk by age ICU – 1 months	0.089588241	0.071670593	0.107505889	Beta
RSV risk by age ICU – 2 months	0.052340965	0.041872772	0.062809158	Beta
RSV risk by age ICU – 3 months	0.018119481	0.014495585	0.021743377	Beta
RSV risk by age ICU – 4 months	0.01092834	0.008742672	0.013114008	Beta
RSV risk by age ICU – 5 months	0.009616369	0.007693095	0.011539643	Beta
RSV risk by age ICU – 6 months	0.005098408	0.004078726	0.00611809	Beta
RSV risk by age ICU – 7 months	0.004599402	0.003679522	0.005519282	Beta
RSV risk by age ICU – 8 months	0.004157479	0.003325983	0.004988975	Beta
RSV risk by age ICU – 9 months	0.004002338	0.00320187	0.004802806	Beta
RSV risk by age ICU – 10 months	0.002486189	0.001988951	0.002983427	Beta
RSV risk by age ICU – 11 months	0.004205399	0.003364319	0.005046479	Beta
RSV risk by age – MV – 0 months	0.008755362	0.007	0.011	Beta
RSV risk by age MV – 1 months	0.019716576	0.018	0.021	Beta

RSV risk by age MV – 2 months	0.015696141	0.014	0.017	Beta
RSV risk by age MV – 3 months	0.003390944	0.002	0.005	Beta
RSV risk by age MV – 4 months	0.002289605	0.001	0.004	Beta
RSV risk by age MV – 5 months	0.001912435	0.000	0.004	Beta
RSV risk by age MV – 6 months	0.002252151	0.001	0.004	Beta
RSV risk by age MV – 7 months	0.001969839	0.000	0.004	Beta
RSV risk by age MV – 8 months	0.001676425	0.000	0.003	Beta
RSV risk by age MV – 9 months	0.001330672	0.000	0.003	Beta
RSV risk by age MV – 10 months	0.000951613	-0.001	0.003	Beta
RSV risk by age MV – 11 months	0.001505135	0.000	0.003	Beta
RSV risk by age – outpatient hospitalisation – 0 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta

RSV risk by age outpatient hospitalisation – 4 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 7 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 10 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta

RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta
RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta
RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta
RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta
RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta

RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta
RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta
RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta
RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta
RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta
RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta

RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age (preterm infant population)				
RSV risk by age – inpatient hospitalisation – 0 months	0.048008746	0.038406997	0.057610495	Beta
RSV risk by age inpatient hospitalisation – 1 months	0.121051239	0.096840991	0.145261487	Beta
RSV risk by age inpatient hospitalisation – 2 months	0.106016015	0.084812812	0.127219218	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.065381574	0.052305259	0.078457889	Beta

RSV risk by age inpatient hospitalisation – 4 months	0.044833109	0.035866487	0.053799731	Beta
RSV risk by age inpatient hospitalisation – 5 months	0.037449802	0.029959842	0.044939762	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.019586394	0.015669115	0.023503673	Beta
RSV risk by age inpatient hospitalisation – 7 months	0.016937811	0.013550249	0.020325373	Beta
RSV risk by age inpatient hospitalisation – 8 months	0.014384521	0.011507617	0.017261425	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.01186651	0.009493208	0.014239812	Beta
RSV risk by age inpatient hospitalisation – 10 months	0.008261728	0.006609382	0.009914074	Beta
RSV risk by age inpatient hospitalisation – 11 months	0.012601799	0.010081439	0.015122159	Beta
RSV risk by age – ICU – 0 months	0.017097786	0.013678229	0.020517343	Beta
RSV risk by age ICU – 1 months	0.027986019	0.022388815	0.033583223	Beta
RSV risk by age ICU – 2 months	0.01635053	0.013080424	0.019620636	Beta

RSV risk by age ICU – 3 months	0.004249912	0.00339993	0.005099894	Beta
RSV risk by age ICU – 4 months	0.002563235	0.002050588	0.003075882	Beta
RSV risk by age ICU – 5 months	0.002255513	0.00180441	0.002706616	Beta
RSV risk by age ICU – 6 months	0.001216808	0.000973446	0.00146017	Beta
RSV risk by age ICU – 7 months	0.001097713	0.00087817	0.001317256	Beta
RSV risk by age ICU – 8 months	0.000992242	0.000793794	0.00119069	Beta
RSV risk by age ICU – 9 months	0.000955215	0.000764172	0.001146258	Beta
RSV risk by age ICU – 10 months	0.000593364	0.000474691	0.000712037	Beta
RSV risk by age ICU – 11 months	0.001003678	0.000802942	0.001204414	Beta
RSV risk by age – MV – 0 months	0.005680392	0.004544314	0.00681647	Beta
RSV risk by age MV – 1 months	0.01037086	0.008296688	0.012445032	Beta
RSV risk by age MV – 2 months	0.004536438	0.00362915	0.005443726	Beta
RSV risk by age MV – 3 months	0.002500267	0.002000214	0.00300032	Beta
RSV risk by age MV – 4 months	0.001307872	0.001046298	0.001569446	Beta
RSV risk by age MV – 5 months	0.000975771	0.000780617	0.001170925	Beta
RSV risk by age MV – 6 months	0.000897453	0.000717962	0.001076944	Beta

RSV risk by age MV – 7 months	0.000944908	0.000755926	0.00113389	Beta
RSV risk by age MV – 8 months	0.000776472	0.000621178	0.000931766	Beta
RSV risk by age MV – 9 months	0	0	0	Beta
RSV risk by age MV – 10 months	0.000314199	0.000251359	0.000377039	Beta
RSV risk by age MV – 11 months	0.000897284	0.000717827	0.001076741	Beta
RSV risk by age – outpatient hospitalisation – 0 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 4 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta

RSV risk by age outpatient hospitalisation – 7 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 10 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta
RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta
RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta

RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta
RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta
RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta
RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta
RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta

RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta
RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta
RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta
RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta

RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age (term infant population)				
RSV risk by age – inpatient hospitalisation – 0 months	0.033909973	0.027127978	0.040691968	Beta
RSV risk by age inpatient hospitalisation – 1 months	0.079869844	0.063895875	0.095843813	Beta
RSV risk by age inpatient hospitalisation – 2 months	0.066080835	0.052864668	0.079297002	Beta
RSV risk by age inpatient hospitalisation – 3 months	0.038239608	0.030591686	0.04588753	Beta
RSV risk by age inpatient hospitalisation – 4 months	0.026038924	0.020831139	0.031246709	Beta
RSV risk by age inpatient hospitalisation – 5 months	0.021716335	0.017373068	0.026059602	Beta
RSV risk by age inpatient hospitalisation – 6 months	0.011409196	0.009127357	0.013691035	Beta

RSV risk by age inpatient hospitalisation – 7 months	0.009925037	0.00794003	0.011910044	Beta
RSV risk by age inpatient hospitalisation – 8 months	0.008421958	0.006737566	0.01010635	Beta
RSV risk by age inpatient hospitalisation – 9 months	0.006734829	0.005387863	0.008081795	Beta
RSV risk by age inpatient hospitalisation – 10 months	0.004793205	0.003834564	0.005751846	Beta
RSV risk by age inpatient hospitalisation – 11 months	0.007455996	0.005964797	0.008947195	Beta
RSV risk by age – ICU – 0 months	0.004830316	0.003864253	0.005796379	Beta
RSV risk by age ICU – 1 months	0.007906364	0.006325091	0.009487637	Beta
RSV risk by age ICU – 2 months	0.004619208	0.003695366	0.00554305	Beta
RSV risk by age ICU – 3 months	0.002045548	0.001636438	0.002454658	Beta
RSV risk by age ICU – 4 months	0.001233724	0.000986979	0.001480469	Beta
RSV risk by age ICU – 5 months	0.001085613	0.00086849	0.001302736	Beta
RSV risk by age ICU – 6 months	0.000649328	0.000519462	0.000779194	Beta
RSV risk by age ICU – 7 months	0.000585775	0.00046862	0.00070293	Beta

RSV risk by age ICU – 8 months	0.000529492	0.000423594	0.00063539	Beta
RSV risk by age ICU – 9 months	0.000509733	0.000407786	0.00061168	Beta
RSV risk by age ICU – 10 months	0.000316638	0.00025331	0.000379966	Beta
RSV risk by age ICU – 11 months	0.000535595	0.000428476	0.000642714	Beta
RSV risk by age – MV – 0 months	0.00125591	0.001004728	0.001507092	Beta
RSV risk by age MV – 1 months	0.002292953	0.001834362	0.002751544	Beta
RSV risk by age MV – 2 months	0.001002987	0.00080239	0.001203584	Beta
RSV risk by age MV – 3 months	0.000470902	0.000376722	0.000565082	Beta
RSV risk by age MV – 4 months	0.000246326	0.000197061	0.000295591	Beta
RSV risk by age MV – 5 months	0.000183778	0.000147022	0.000220534	Beta
RSV risk by age MV – 6 months	0.000202832	0.000162266	0.000243398	Beta
RSV risk by age MV – 7 months	0.000213558	0.000170846	0.00025627	Beta
RSV risk by age MV – 8 months	0.00017549	0.000140392	0.000210588	Beta
RSV risk by age MV – 9 months	0	0	0	Beta
RSV risk by age MV – 10 months	7.10117E-05	5.68094E-05	8.5214E-05	Beta
RSV risk by age MV – 11 months	0.000202794	0.000162235	0.000243353	Beta

RSV risk by age – outpatient hospitalisation – 0 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 1 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 2 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 3 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 4 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 5 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 6 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 7 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 8 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 9 months	0	0	0	Beta

RSV risk by age outpatient hospitalisation – 10 months	0	0	0	Beta
RSV risk by age outpatient hospitalisation – 11 months	0	0	0	Beta
RSV risk by age – ER visit – 0 months	0.01274	0.010192	0.015288	Beta
RSV risk by age - ER visit – 1 months	0.04173	0.033384	0.050076	Beta
RSV risk by age - ER visit – 2 months	0.04706	0.037648	0.056472	Beta
RSV risk by age - ER visit – 3 months	0.06838	0.054704	0.082056	Beta
RSV risk by age - ER visit – 4 months	0.0754	0.06032	0.09048	Beta
RSV risk by age - ER visit – 5 months	0.046345	0.037076	0.055614	Beta
RSV risk by age - ER visit– 6 months	0.0409	0.03272	0.04908	Beta
RSV risk by age - ER visit – 7 months	0.02805	0.02244	0.03366	Beta
RSV risk by age - ER visit – 8 months	0.0278	0.02224	0.03336	Beta
RSV risk by age - ER visit – 9 months	0.0278	0.02224	0.03336	Beta

RSV risk by age - ER visit – 10 months	0.0202	0.01616	0.02424	Beta
RSV risk by age - ER visit – 11 months	0.0278	0.02224	0.03336	Beta
RSV risk by age – PC visit – 0 months	0.096994031	0.077595225	0.116392837	Beta
RSV risk by age - PC visit – 1 months	0.218425031	0.174740025	0.262110037	Beta
RSV risk by age - PC visit – 2 months	0.173885673	0.139108538	0.208662808	Beta
RSV risk by age - PC visit – 3 months	0.09883675	0.0790694	0.1186041	Beta
RSV risk by age - PC visit – 4 months	0.066735747	0.053388598	0.080082896	Beta
RSV risk by age - PC visit – 5 months	0.055742252	0.044593802	0.066890702	Beta
RSV risk by age - PC visit – 6 months	0.034309367	0.027447494	0.04117124	Beta
RSV risk by age - PC visit – 7 months	0.030008616	0.024006893	0.036010339	Beta
RSV risk by age - PC visit – 8 months	0.025538733	0.020430986	0.03064648	Beta
RSV risk by age - PC visit – 9 months	0.020271521	0.016217217	0.024325825	Beta

RSV risk by age - PC visit – 10 months	0.014496916	0.011597533	0.017396299	Beta
RSV risk by age - PC visit – 11 months	0.022929289	0.018343431	0.027515147	Beta
RSV risk by age – URTI – 0 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 1 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 2 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 3 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 4 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 5 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 6 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 7 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 8 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 9 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 10 months	0.078067606	0.062454085	0.093681127	Beta
RSV risk by age - URTI – 11 months	0.078067606	0.062454085	0.093681127	Beta
Coverage rate palivizumab eligible population				

Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of Palivizumab – January	0.58	0.464	0.696	Normal

Coverage rate of Palivizumab – February	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – March	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – April	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – May	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – June	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – July	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – August	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – September	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – October	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – November	0.58	0.464	0.696	Normal
Coverage rate of Palivizumab – December	0.58	0.464	0.696	Normal
Coverage rate preterm infant population				
Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal

Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of Palivizumab – January	0	0	0	Normal
Coverage rate of Palivizumab – February	0	0	0	Normal

Coverage rate of Palivizumab – March	0	0	0	Normal
Coverage rate of Palivizumab – April	0	0	0	Normal
Coverage rate of Palivizumab – May	0	0	0	Normal
Coverage rate of Palivizumab – June	0	0	0	Normal
Coverage rate of Palivizumab – July	0	0	0	Normal
Coverage rate of Palivizumab – August	0	0	0	Normal
Coverage rate of Palivizumab – September	0	0	0	Normal
Coverage rate of Palivizumab – October	0	0	0	Normal
Coverage rate of Palivizumab – November	0	0	0	Normal
Coverage rate of Palivizumab – December	0	0	0	Normal
Coverage rate term infant population				
Coverage rate of nirsevimab – January	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – February	0.8	0.64	0.96	Normal

Coverage rate of nirsevimab – March	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – April	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – May	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – June	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – July	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – August	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – September	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – October	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – November	0.8	0.64	0.96	Normal
Coverage rate of nirsevimab – December	0.8	0.64	0.96	Normal
Coverage rate of Palivizumab – January	0	0	0	Normal
Coverage rate of Palivizumab – February	0	0	0	Normal
Coverage rate of Palivizumab – March	0	0	0	Normal

Coverage rate of Palivizumab – April	0	0	0	Normal
Coverage rate of Palivizumab – May	0	0	0	Normal
Coverage rate of Palivizumab – June	0	0	0	Normal
Coverage rate of Palivizumab – July	0	0	0	Normal
Coverage rate of Palivizumab – August	0	0	0	Normal
Coverage rate of Palivizumab – September	0	0	0	Normal
Coverage rate of Palivizumab – October	0	0	0	Normal
Coverage rate of Palivizumab – November	0	0	0	Normal
Coverage rate of Palivizumab – December	0	0	0	Normal
RSV complication risk				
Risk of complication – Recurrent wheezing: palivizumab eligible population	0.31	0.248	0.372	Beta
Risk of complication Recurrent wheezing:	0.31	0.248	0.372	Beta

preterm infant population				
Risk of complication Recurrent wheezing: term infant population	0.31	0.248	0.372	Beta
Risk of complication – Asthma: palivizumab eligible population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication Asthma: preterm infant population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication Asthma: term infant population	0.106382979	0.085106383	0.127659575	Beta
Risk of complication – Excess HCRU: palivizumab eligible population	0.1	0.08	0.12	Beta
Risk of complication Excess HCRU: preterm infant population	0.1	0.08	0.12	Beta
Risk of complication Excess HCRU: term infant population	0.1	0.08	0.12	Beta
Risk of complication – Otis Media: palivizumab eligible population	0.1	0.08	0.12	Beta
Risk of complication Otis	0.1	0.08	0.12	Beta

Media: preterm infant population				
Risk of complication Otis Media: term infant population	0.1	0.08	0.12	Beta
Risk of complication – Recurrent wheezing /year 2: palivizumab eligible population	0.27	0.216	0.324	Beta
Risk of complication Recurrent wheezing /year 2: preterm infant population	0.27	0.216	0.324	Beta
Risk of complication Recurrent wheezing /year 2: term infant population	0.27	0.216	0.324	Beta
Risk of complication – Recurrent wheezing /year 3: palivizumab eligible population	0.17	0.136	0.204	Beta
Risk of complication Recurrent wheezing /year 3: preterm infant population	0.17	0.136	0.204	Beta
Risk of complication Recurrent wheezing /year 3: term infant population	0.17	0.136	0.204	Beta
RSV mortality risk				

RSV mortality risk (per case): palivizumab eligible population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): palivizumab eligible population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): palivizumab eligible population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): preterm infant population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): term infant population – 0-5 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): term infant population – 6-11 months	4.94E-04	0.0003952	0.0005928	Beta
RSV mortality risk (per case): term infant population – 12-59 months	4.94E-04	0.0003952	0.0005928	Beta

Disutilities				
Disutility associated with RSV event				
Hospitalizations (incl. ICU admission and MV)	0.01014	0.008112	0.012168	Beta
Intensive care or observation: Conditional on Initial Hospitalization	0.01014	0.008112	0.012168	Beta
Mechanical ventilation: Conditional on Initial Hospitalization	0.01014	0.008112	0.012168	Beta
Pediatric emergency admission (akut børnemodtagelse)	0.00630	0.00504	0.00756	Beta
Primary care visits	0.00630	0.00504	0.00756	Beta
Open hospitalisation "åben indlæggelse"	0.00382	0.003056	0.004584	Beta
All-cause LRTI hospitalizations (excl. RSV)	0.00382	0.003056	0.004584	Beta
Parent/caregiver QALY loss	0.00074	0.000592	0.000888	Beta
Costs				
RSV treatment cost: Palivizumab eligible population				
Hospitalizations Alone	219171	175336.8	263005.2	Gamma
Intensive care or observation: Conditional on	245958	196766.4	295149.6	Gamma

Initial Hospitalization				
Mechanical ventilation (incl. hospitalization and ICU)	435033	348026.4	522039.6	Gamma
Pediatric emergency admission (akut børnemodtagelse)	3321	2656.8	3985.2	Gamma
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation "åben indlæggelse"	3321	2656.8	3985.2	Gamma
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV treatment cost: Preterm infant population				
Hospitalizations Alone	126168	100934.4	151401.6	Gamma
Intensive care or observation: Conditional on Initial Hospitalization	160154.5	128123.6	192185.4	Gamma
Mechanical ventilation (incl. hospitalization and ICU)	263628	210902.4	316353.6	Gamma
Pediatric emergency admission (akut børnemodtagelse)	3321	2656.8	3985.2	Gamma
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation	3321	2656.8	3985.2	Gamma

"åben indlæggelse"				
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV treatment cost: Term infant population				
Hospitalizations Alone	20868	16694.4	25041.6	Gamma
Intensive care or observation: Conditional on Initial Hospitalization	54129	43303.2	64954.8	Gamma
Mechanical ventilation (incl. hospitalization and ICU)	180448	144358.4	216537.6	Gamma
Pediatric emergency admission (akut børnemodtagelse)	3321	2656.8	3985.2	Gamma
Primary care visits	153.61	122.888	184.332	Gamma
Open hospitalisation "åben indlæggelse"	3321	2656.8	3985.2	Gamma
All-cause LRTI hospitalizations (excl. RSV)	11748	9398.4	14097.6	Gamma
RSV complication management cost: Palivizumab eligible population				
Recurrent wheezing	844.855	844.855	844.855	Gamma
Asthma	844.855	844.855	844.855	Gamma
Excess HCRU	0	0	0	Gamma

Otitis media	0	0	0	Gamma
Recurrent Wheezing (Year 2)	816.2850242	816.2850242	816.2850242	Gamma
Recurrent Wheezing (Year 3)	788.6811828	788.6811828	788.6811828	Gamma
RSV complication management cost: Preterm infant population				
Recurrent wheezing	844.855	675.884	1013.826	Gamma
Asthma	844.855	675.884	1013.826	Gamma
Excess HCRU	0	0	0	Gamma
Otitis media	0	0	0	Gamma
Recurrent Wheezing (Year 2)	816.2850242	653.0280194	979.542029	Gamma
Recurrent Wheezing (Year 3)	788.6811828	630.9449462	946.4174194	Gamma
RSV complication management cost: Term infant population				
Recurrent wheezing	844.855	844.855	844.855	Gamma
Asthma	844.855	844.855	844.855	Gamma
Excess HCRU	0	0	0	Gamma
Otitis media	0	0	0	Gamma
Recurrent Wheezing (Year 2)	816.2850242	816.2850242	816.2850242	Gamma
Recurrent Wheezing (Year 3)	788.6811828	788.6811828	788.6811828	Gamma

Abbreviations: RSV= respiratory syncytial virus, ICU= intensive care unit (refers to intensive observation and care), MV= mechanical ventilation, ER= emergency room (refers to pediatric emergency admission (akut

børnemodtagelse), PC= primary care, URTI= upper respiratory tract infection, HCRU= healthcare resource use, LRTI= lower respiratory tract infection , QALY= quality-adjusted life-years

Notes: Discount rates for year 1 (is 1 because this is the current year, hence no need for discounting costs and outcomes). 3.5% is applied as discount rate for both costs and outcomes: Year 1: 1 / (1+0.035)*(1-1), Year 2: 1 / (1+0.035)^(2-1) = 0.9666, Year 3: (1+0.035)^(3-1) = 0.93333

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

An SLR was conducted which aimed to address the following research question:
To evaluate and summarise evidence on the efficacy, safety, and tolerability of nirsevimab and Abrysvo for the prevention of medically attended RSV infection in infants.

This SLR was performed in three stages: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; a systematic selection of the relevant studies based on explicit inclusion and exclusion criteria; and an extraction of relevant data from eligible studies to assess clinical evidence across various therapeutic options.

This SLR included searches of the following electronic databases as standard evidence sources for clinical data used in international HTAs:

- Embase® and MEDLINE® (via Ovid.com)
- MEDLINE® In-Process (via Ovid.com)
- The Cochrane Library (via cochranelibrary.com), including the following:
    - The Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)

Electronic searching in the literature databases was not limited according to timeframe because clinical outcomes are unlikely to change with time; however as both nirsevimab and Abrysvo are relatively new treatments, the impact of restricting by timeframe would probably be very minor.

Bibliographies of systematic reviews were screened to ensure that initial searches captured all the relevant clinical studies. No language restrictions were applied.

The records identified through electronic and manual searches were supplemented by records identified from trial registry websites. The following clinical trial registries were searched:

- Clinicaltrials.gov (https://clinicaltrials.gov/)
- EU Clinical Trial Register (https://www.clinicaltrialsregister.eu/)

Table 85 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	Inception to date of search	12.02.2024
Medline	Ovid	Inception to date of search	12.02.2024
MEDLINE In-Process	Ovid	Inception to date of search	12.02.2024
CDSR	cochranelibrary.com	Inception to date of search	12.02.2024
CENTRAL	cochranelibrary.com	Inception to date of search	12.02.2024

Conference abstract were captured through Embase searches.

Table 86 Other sources included in the literature search

Source name	Location/source	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	22.02.2024
EU Clinical Trial Register	https://www.clinicaltrialsregister.eu/	22.02.2024

H.1.1 Search strategies

The search strategies employed in the SLR are provided in Table 87, Table 88, Table 89, Table 90, and Table 91.

Table 87 Search strategy for Embase (OVID, February 12th, 2024)

No.	Query	Results
	RS Virus	
1	exp 'human respiratory syncytial virus'/	9503
2	exp 'respiratory syncytial virus infection'/	8433
3	exp 'respiratory tract infection'/	507549
4	exp 'bronchiolitis'/	27026
5	exp 'pneumonia'/	406884
6	exp 'pneumovirus'/	10097

7	('respiratory syncytial virus*' or rsv).ab,kw,ti.	28681
8	bronchiolit*.ab,kw,ti.	20881
9	(pneumon* or bronchopneumon* or pleuropneumon*).ab,kw,ti.	350308
10	('lower respiratory infection*' or 'lower respiratory tract infection*' or lrti).ab,kw,ti.	14871
11	acute respiratory infection*.ab,kw,ti.	7368
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	907487
	Nirsevimab	
13	exp 'nirsevimab'/	216
14	(nirsevimab or beyfortus or MEDI8897 or MEDI-8897).ab,kw,ti.	137
15	13 or 14	231
	Abrysvo	
16	exp 'pf 06928316'/	17
17	('pf 06928316' or pf06928316 or pf6928316 or abrysvo or rsvpref).ab,kw,ti.	33
18	16 or 17	41
	('RS virus' AND 'nirsevimab') OR ('RS virus' AND 'Abrysvo')	
19	12 and 15	215
20	12 and 18	40
21	19 or 20	239

Table 88. Search strategy for MEDLINE (OVID, February 12th, 2024)

No.	Query	Results
	RS Virus	
1	exp respiratory syncytial virus, human/	4211
2	exp respiratory syncytial virus infections/	8997
3	exp respiratory tract infections/	641875
4	exp bronchiolitis/	10090
5	exp pneumonia/	356453
6	exp pneumovirus/	11198
7	('respiratory syncytial virus*' or rsv).ab,kw,ti.	22431
8	bronchiolit*.ab,kw,ti.	13302
9	(pneumon* or bronchopneumon* or pleuropneumon*).ab,kw,ti.	251026
10	('lower respiratory infection*' or 'lower respiratory tract infection*' or lrti).ab,kw,ti.	10163
11	acute respiratory infection*.ab,kw,ti.	5903
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	822029
	Nirsevimab	

13	(nirsevimab or beyfortus or MEDI8897 or MEDI-8897).ab,kw,ti.	101
	Abrysvo	
14	('pf 06928316' or pf06928316 or pf6928316 or abrysvo or rsvpref).ab,kw,ti.	27
	('RS virus' AND 'nirsevimab') OR ('RS virus' AND 'Abrysvo')	
15	12 and 13	98
16	12 and 14	27
17	15 or 16	116

Table 89. Search strategy for CENTRAL (Cochrane Library, February 12th, 2024)

No.	Query	Results
	RS Virus	
#1	MeSH descriptor: [Respiratory Syncytial Virus, Human] explode all trees	139
#2	MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees	509
#3	MeSH descriptor: [Respiratory Tract Infections] explode all trees	26828
#4	MeSH descriptor: [Bronchiolitis] explode all trees	718
#5	MeSH descriptor: [Pneumonia] explode all trees	12316
#6	MeSH descriptor: [Pneumovirus] explode all trees	292
#7	('respiratory syncytial virus*' or rsv):ti,ab,kw (Word variations have been searched)	1498
#8	(bronchiolit*):ti,ab,kw (Word variations have been searched)	1728
#9	(pneumon* or bronchopneumon* or pleuropneumon):ti,ab,kw (Word variations have been searched)	25617
#10	('lower respiratory infection*' or 'lower respiratory tract infection*' or lrti):ti,ab,kw (Word variations have been searched)	5484
#11	('acute respiratory infection*'):ti,ab,kw (Word variations have been searched)	6982
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	52735
	Nirsevimab	
#13	(nirsevimab or beyfortus or MEDI8897 or MEDI-8897):ti,ab,kw	31
	Abrysvo	
#14	('pf 06928316' or pf06928316 or pf6928316 or abrysvo or rsvpref):ti,ab,kw	26
	('RS virus' AND 'nirsevimab') OR ('RS virus' AND 'Abrysvo')	
#15	#12 and #13	30
#16	#12 and #14	24
#17	#15 or #16	54

Table 90. Search strategy for Clinicaltrials.gov (https://clinicaltrials.gov, February 22nd, 2024)

S. No.	Query	Results
	Nirsevimab	
#1	nirsevimab OR beyfortus OR MEDI8897 OR MEDI-8897	15
	Abrysvo	
#2	pf 06928316 OR pf06928316 OR pf6928316 OR abrysvo OR rsvpref	30

Table 91. Search strategy for EUCTR (https://clinicaltrialsregister.eu, February 22nd, 2024)

S. No.	Query	Results
	Nirsevimab	
#1	nirsevimab OR beyfortus OR MEDI8897 OR MEDI-8897	6
	Abrysvo	
#2	abrysvo OR rsvpref*	3

H.1.2 Systematic selection of studies

All retrieved studies were assessed against the eligibility criteria, detailed in Table 92. Primary (Level 1) screening were performed by two independent NHTA reviewers who reviewed each reference (title and abstract) identified in the literature search, applied basic study selection criteria (population, intervention, and study design), and decided on whether to include or exclude the study reference at this stage. Any uncertainty regarding the inclusion of studies were resolved through discussion, if necessary, involving a third reviewer.

For secondary (Level 2) screening of potentially relevant articles, the full articles were obtained. These were independently reviewed by two independent reviewers against each eligibility criterion. Any uncertainty regarding the inclusion of studies were resolved through discussion, if necessary, involving a third reviewer.

As mentioned above, bibliographies of key published systematic reviews were also screened to ensure that initial searches captured all the relevant studies.

During the screening, a record was of all included and excluded articles and the reasons for these decisions; these are summarised in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart, as seen Figure 22. All studies excluded at the full-text screening stage are provided, alongside reasons for exclusion in Table 95.

Table 92. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Infants or children under two years of age, regardless of risk factors	Children over two years of age or adults

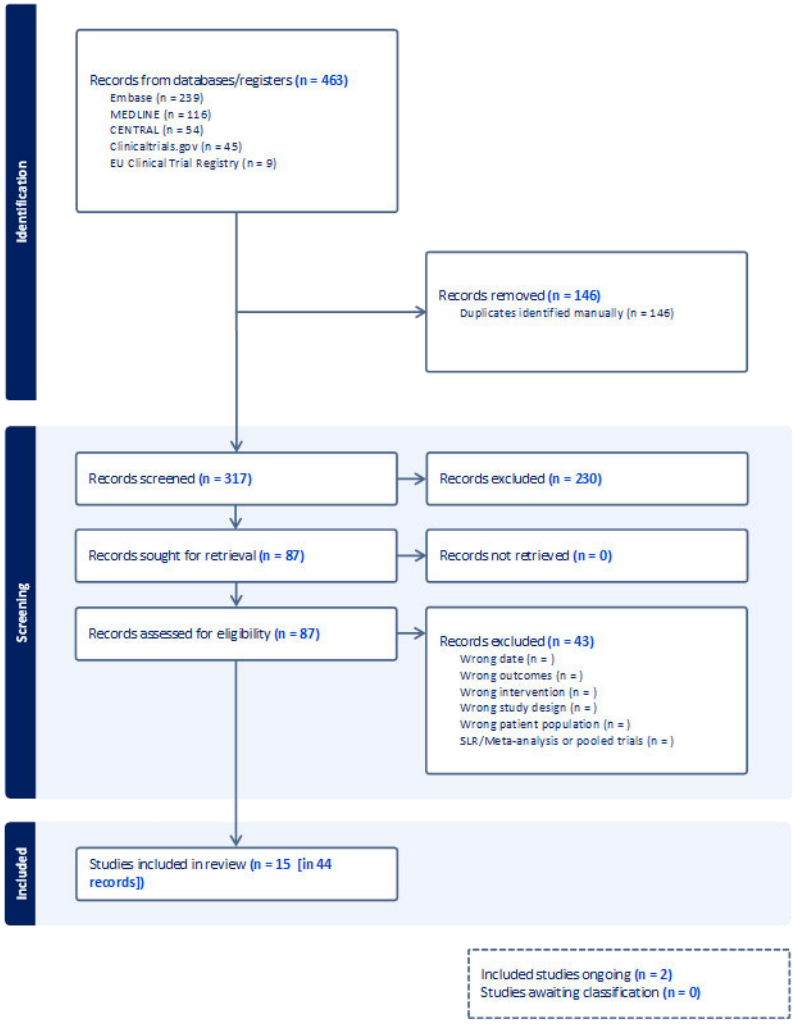
Interventions	Nirsevimab Abrysvo	Studies not examining either nirsevimab or Abrysvo
Comparators	Placebo Palivizumab No comparator	
Outcomes	Efficacy: RSV LRTI infections (clinical diagnoses or RT-PCR confirmed) Medically attended RSV infections, including: • Primary care visits due to RSV • Emergency room visits due to RSV • Hospitalisations due to RSV (including duration of hospitalisation) • ICU treatment due to RSV (including duration of ICU treatment) • Mechanical ventilation due to RSV (including duration of mechanical ventilation) Medically attended LRTI due to any cause Health-related quality of life Safety: Treatment-emergent adverse events Treatment-related adverse events Treatment-emergent serious adverse events Treatment-related serious adverse events	All other outcomes
Study type	Randomised controlled trials Non-randomised controlled trials Single-arm trials Retrospective and prospective cohort studies	Letters, comments, and editorials Cross-sectional studies, Case studies or case reports Systematic reviews* Health economic evaluations*

Language	No restrictions
Countries	No restrictions
Time limit	No restrictions

Abbreviations: LRTI= Lower respiratory tract infection, RSV= respiratory syncytial virus, RT-PCR= Reverse transcriptase-polymerase chain reaction

Notes: *Health economic evaluations and ystematic reviews will not be included, but will be flagged for bibliography searches

Figure 22. PRISMA flowchart for SLR of nirsevimab and Abrysvo



The studies included in the broad SLR are shown in . Due to the large number of randomised trials identified, phase 1 studies, observational studies, and studies only examining safety (except MEDLEY, which informs the safety of nirsevimab in the palivizumab-eligible population specifically) were not included in this submission. These studies are shown in Table 93.

Table 93. Studies identified in broad SLR, not included in submission

STUDY ID	Study design	Identified records	Reason for not including in submission
NCT02290340	Phase 1b/2a, randomised, double-blind, placebo-controlled, dose-escalation study	Domachowske JB, Khan AA, Jensen K, et al. A single dose monoclonal antibody immunoprophylaxis strategy to prevent respiratory syncytial virus disease in all infants: results of the first in infant study with MEDI8897. Pediatrics 2018; 141(1). Domachowske JB, Khan A, Esser MT, et al. A single dose monoclonal antibody (MAB) immunoprophylaxis strategy to prevent RSV disease in all infants: results of the first in infant study with medi8897. Open forum infectious diseases 2017; 4: S37. Domachowske JB, Khan AA, Esser MT, et al. Safety, Tolerability and Pharmacokinetics of MEDI8897, an Extended Half-life Single-dose Respiratory Syncytial Virus Prefusion F-targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants. *Pediatric infectious disease journal* 2018; **37**(9): 886-92.	Phase 1b/2a and no pre-defined efficacy outcomes
MUSIC (NCT04484935)	Phase 2, open-label, uncontrolled, single-dose study	https://classic.clinicaltrials.gov/ct2/show/NCT04484935	Uncontrolled study, only safety outcomes
CHIMES (NCT05110261)	Phase 3, randomised, double-blind, placebo-controlled study	https://classic.clinicaltrials.gov/ct2/show/NCT05110261	Study ongoing, with no results published. Only includes Chinese infants
JUBILUS (NCT06042049)	Phase 3, single-arm, open-label study	https://classic.clinicaltrials.gov/ct2/show/NCT06042049	Study ongoing, with no results published. Single-arm study. Only includes Japanese infants

Lopez-Lacort et al 2024	Observational study - Spain	Lopez-Lacort M, Munoz-Quiles C, Mira-Iglesias A, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2024; 29(6).	Observational study
Ernst et al. 2024	Observational study – Luxembourg	Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2024; **29**(4).	Observational study
NCT06172660	Observational study – USA	https://classic.clinicaltrials.gov/show/NCT06172660	Observational study – no results published
NIRSE-GAL	Observational study - USA	https://classic.clinicaltrials.gov/show/NCT06180993 *Note: NIRSE-GAL results were published by Ares-Gomez et al. after the search dates for the SLR:* Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. The Lancet Infectious Diseases 2024.	Observational study
ENVIE	Observational study – France	https://classic.clinicaltrials.gov/ct2/show/NCT06030505	Observational study – no results published

The studies included in this submission are shown in .

Table 94. Studies from the broad SLR, included in the submission

References	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. New England journal of medicine 2022; 386(9): 837-46.[7] Muller WJ, Madhi SA, Seoane Nunez B, et al. Nirsevimab for Prevention of RSV in Term and Late-Preterm Infants. New England Journal of Medicine 2023; 388(16): 1533-4. Ahani B, Tuffy KM, Aksyuk AA, et al. Molecular and phenotypic characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. Nature communications 2023; 14(1): 4347. Dagan R, Hammitt LL, Seoane Nunez B, et al. Infants Receiving a	MELODY	NCT03979313	Start: 23/7/2019 Completion: 21/3/2023 Data cut-off: Final Future data cut-offs: None	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo

References	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Single Dose of Nirsevimab to Prevent RSV Do Not Have Evidence of Enhanced Disease in their Second RSV Season. J Pediatric Infect Dis Soc 2024; 14: 14. Clinicaltrials.gov entry EUCTR entry WHO ICTRP entry				
Griffin MP, Yuan Y, Takas T, et al. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. New England journal of medicine 2020; 383(5): 415-25.[84] Griffin MP, Yuan Y, Takas T, et al. MEDI8897 prevents serious RSV disease in healthy preterm infants. Open forum infectious diseases 2019; 6: S27. Ahani B, Tuffy KM, Aksyuk AA, et al. Molecular and phenotypic	Griffin et al. 2020	NCT02878330	Start: 3/11/2016 Completion: 17/7/2018 Data cut-off: Final Future data cut-offs: None	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo

References	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
characteristics of RSV infections in infants during two nirsevimab randomized clinical trials. Nature communications 2023; 14(1): 4347. Madhi SA, Simões EAF. Single-dose nirsevimab prevents RSV infection. Journal of pediatrics 2021; 228: 310-3. Clinicaltrials.gov entry EUCTR entry				
Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. New England journal of medicine 2023; 389(26): 2425-35.[9] Clinicaltrials.gov entry EUCTR entry WHO ICTRP entry	HARMONIE	NCT05437510	Start: 8/8/2022 Completion: 14/3/2025 Data cut-off: Interim Analysis Future data cut-offs: Final data upon completion	Safety and efficacy of nirsevimab versus placebo for the prevention of RSV Indirect comparison of nirsevimab versus Abrysvo

References	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Domachowske J, Madhi SA, Simões EAF, et al. Safety of Nirsevimab for RSV in Infants with Heart or Lung Disease or Prematurity. New England journal of medicine 2022; 386(9): 892-4.[85] Clinicaltrials.gov entry EUCTR entry WHO ICTRP entry	MEDLEY	NCT03959488	Start: 30/7/2019 Completion: 20/1/2023 Data cut-off: Final Future data cut-offs: None	Safety of nirsevimab versus palivizumab for the prevention of RSV in palivizumab-eligible infants
Simões EAF, Tita ATN, Swanson KA, et al. Prefusion F Protein-Based Respiratory Syncytial Virus Immunization in Pregnancy. *New England journal of medicine* 2022; 386(17): 1615-26.[10] Simoes EAF, Madhi SA, Llapur CJ, et al. Establishing Proof of Concept for a Bivalent RSVpreF Subunit Vaccine for Maternal Immunization. *Open forum*	Simoes et al. 2022	NCT04032093	Start: 7/8/2023 Completion: 30/9/2021 Data cut-off: Unclear Future data cut-offs: Unclear	Indirect comparison of nirsevimab versus Abrysvo

References	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
infectious diseases 2022; **9**: S13.				
Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. New England journal of medicine 2023; 388(16): 1451-64.[3] Clinicaltrials.gov entry EUCTR.gov entry	MATISSE	NCT04424316	Start: 17/20/2020 Completion: 27/10/2023 Data cut-off: Interim analysis Future data cut-offs: Unclear	Indirect comparison of nirsevimab versus Abrysvo

Studies excluded at the full-text screening stage are shown in Table 95.

Table 95. Records excluded at full-text screening stage

Reference	Reason for exclusion
Lorenz J. Neonatology: RSV prophylaxis with nirsevimab in late-preterm and term infants. [German]. Zeitschrift fur Geburtshilfe und Neonatologie 2022; 226(4): 224-5.	Wrong publication type
Anonymous. Single-dose nirsevimab protects preterm infants against respiratory syncytial virus infection. [German]. Zeitschrift fur Geburtshilfe und Neonatologie 2020; 224(5): 241-2.	Wrong publication type
Lai X, Ma Y, Zou W, Soudani S, Fang H. EPH206 Public Health Impact of Nirsevimab Against Lower Respiratory Infections Associated with Respiratory Syncytial Virus Among Chinese Infants. *Value in Health* 2023; **26(12 Supplement)**: S241.	Wrong study design
Kieffer A, Ghemmouri M, Hodges E, et al. EPH154 Modeled Head-to-Head Comparison of Nirsevimab and Rsvpref Maternal Vaccine in the US. *Value in Health* 2023; **26(12 Supplement)**: S232.	Wrong study design
Goyette A, Averin A, Atwood M, et al. EPH102 Potential Public Health Impact of Bivalent Respiratory Syncytial Virus Prefusion F (RSVpreF) Maternal Vaccine for Prevention of Respiratory Syncytial Virus (RSV) Lower Respiratory Tract Illness (LRTI) Among Canadian Infants. *Value in Health* 2023; **26(12 Supplement)**: S221-S2.	Wrong study design
Farid AT, Hariharan D, Shepard DS. EPH72 Potential Adverse Effects of Passive Immunization Against Respiratory Syncytial Virus (RSV) in Low-Risk Infants in the United States. *Value in Health* 2022; **25(7 Supplement)**: S448.	Wrong study design

Falavigna M, Watanabe SF, Santoro J, et al. Modelled Impact of Nirsevimab for All Infants in the Prevention of Respiratory Syncytial Virus (RSV): Related Hospitalizations and Its Predicted Cost to the Brazilian Public Healthcare System. *Value in Health* 2023; **26(12 Supplement)**: S26.	Wrong study design
Falavigna M, Watanabe SF, Santoro J, et al. CO103 Modelled Impact of Nirsevimab for All Infants in Preventing Respiratory Syncytial Virus (RSV): Related Hospitalizations and Costs in the Brazilian Private Healthcare System. *Value in Health* 2023; **26(12 Supplement)**: S33.	Wrong study design
Bini C, Marcellusi A, Muzii B, et al. EE696 Economic and Clinical Burden Associated with Respiratory Syncytial Virus (RSV) and Expected Impact of Universal Immunization with Nirsevimab Among All Infants in Their First Rsv Season Against Standard of Care in Italy. *Value in Health* 2023; **26(12 Supplement)**: S188.	Wrong study design
Beuvelet M, Hoestlandt C, Lemaitre M, Demont C, Kieffer A. POSB191 Modeled Impact of Nirsevimab Against Respiratory Syncytial Virus (RSV) Among French Infants Experiencing Their First RSV Season. *Value in Health* 2022; **25(1 Supplement)**: S131.	Wrong study design
Beuvelet M, Davidson C, Hudson R, Kieffer A. POSA197 Modeled Impact of Nirsevimab Against Respiratory Syncytial Virus (RSV) Among UK Infants Experiencing Their First RSV Season. *Value in Health* 2022; **25(1 Supplement)**: S125.	Wrong study design
Beuvelet M, Chung-Delgado K, Kieffer A. PIN29 Cost-Effectiveness of Nirsevimab Against Respiratory Syncytial VIRUS (RSV) Among US Infants Experiencing Their First RSV Season. *Value in Health* 2021; **24(Supplement 1)**: S110.	Wrong study design
Hodgson D, Koltai M, Krauer F, Flasche S, Jit M, Atkins KE. Optimal Respiratory Syncytial Virus intervention programmes using Nirsevimab in England and Wales. *Vaccine* 2022; **40**(49): 7151-7.	Wrong study design
Do LAH, Le NTN, Mahmud S, Mulholland K, Pecenka C, Clark A. Impact and cost-effectiveness of strategies to prevent respiratory syncytial virus (RSV) disease in Vietnam: A modelling study. *Vaccine* 2023; **41(46)**: 6782-90.	Wrong study design

Strine MS, Wilen CB. Game over for RSV? *Sci Immunol* 2023; **8**(84): eadi8764.	Wrong publication type
Karron RA. Preventing respiratory syncytial virus (RSV) disease in children. *Science* 2021; **372(6543)**: 686-7.	Wrong study design
Langedijk AC, Harding ER, Konya B, et al. A systematic review on global RSV genetic data: Identification of knowledge gaps. *Rev Med Virol* 2022; **32**(3): e2284.	Wrong study design
Anonymous. Nirsevimab (Beyfortus) to prevent RSV infection in infants. *Prescrire International* 2023; **32(254)**: 285-7.	Wrong study design
Robinson J. Monoclonal antibody 75% effective in infants against respiratory viral infection. *Pharmaceutical Journal* 7959; **308**(7959).	Wrong publication type
Yu T, Padula WV, Yieh L, Gong CL. Cost-effectiveness of nirsevimab and palivizumab for respiratory syncytial virus prophylaxis in preterm infants 29-34 6/7 weeks' gestation in the United States. *Pediatr neonatol* 2023; **11**: 11.	Wrong study design
Abram ME, Ahani B, Tabor DE, et al. Pooled analysis of nirsevimab resistance through 150 days post dose in preterm and term infants. *Open Forum Infectious Diseases* 2022; **9(Supplement 2)**: S14.	Wrong study design
O'Leary K. Tackling the burden of RSV. *Nature Medicine* 2022; **28(12)**: 2449.	Wrong publication type
Shoukat A, Abdollahi E, Galvani AP, Halperin SA, Langley JM, Moghadas SM. Cost-Effectiveness Analysis of Nirsevimab and RSVpreF Vaccine Prevention Strategies for Respiratory Syncytial Virus Disease in infants: A Canadian Immunisation Research Network (CIRN) Study. *medRxiv* 2023; **16**.	Wrong study design

Shoukat A, Abdollahi E, Galvani AP, Halperin SA, Langley JM, Moghadas SM. Cost-effectiveness analysis of nirsevimab and maternal RSVpreF vaccine strategies for prevention of Respiratory Syncytial Virus disease among infants in Canada: a simulation study. *Lancet Regional Health - Americas* 2023; **28(no pagination)**.	Wrong study design
Simoes EAF, Madhi SA, Muller WJ, et al. 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. *The Lancet Child and Adolescent Health* 2023; **7(3)**: 180-9.	Wrong study design
Ramilo O, Rodriguez-Fernandez R, Mejias A. Respiratory Syncytial Virus Infection: Old Challenges and New Approaches. *Journal of Infectious Diseases* 2023; **228(1)**: 4-7.	Wrong publication type
Kieffer A, Beuvelet M, Sardesai A, et al. Expected Impact of Universal Immunization With Nirsevimab Against RSV-Related Outcomes and Costs Among All US Infants in Their First RSV Season: A Static Model. *Journal of Infectious Diseases* 2022; **226**(Suppl 2): S282-S92.	Wrong study design
Scotta MC, Stein RT. Current strategies and perspectives for active and passive immunization against Respiratory Syncytial Virus in childhood. *J Pediatr (Rio J)* 2023; **99 Suppl 1**: S4-S11.	Wrong study design
Sun M, Lai H, Na F, et al. Monoclonal Antibody for the Prevention of Respiratory Syncytial Virus in Infants and Children: A Systematic Review and Network Meta-analysis. *JAMA netw* 2023; **6**(2): e230023.	Wrong study design
EUCTR. Clinical Study to Evaluate the Safety and Efficacy of MEDI8897, an Experimental Drug, for Preventing Serious Respiratory Syncytial Virus Disease in Healthy Late Preterm and Term Infants. https://trialsearchwhoint/Trial2aspx?TrialID=EUCTR2019-000114-11-PL 2019.	Duplicate
Aragona E, Joshi NS, Birnie KL, Lysouvakon P, Basuray RG. Early Experiences With Nirsevimab: Perspectives From Newborn Hospitalists. *Hosp* 2023; **20**: 20	Wrong publication type

Turalde-Mapili MWR, Mapili JAL, Turalde CWR, Pagcatipunan MR. The efficacy and safety of nirsevimab for the prevention of RSV infection among infants: A systematic review and meta-analysis. *Front* 2023; **11**: 1132740.	Wrong study design
Bergeron HC, Tripp RA. Breakthrough therapy designation of nirsevimab for the prevention of lower respiratory tract illness caused by respiratory syncytial virus infections (RSV). *Expert Opin Investig Drugs* 2022; **31**(1): 23-9.	Wrong publication type
Murphy S. Nirsevimab reduces medically attended RSV-associated lower respiratory tract infection and hospitalisations in healthy pre-term infants. *Arch* 2022; **107**(4): 310-1.	Wrong publication type
Iofrio de Arce A, Alvarez Garcia FJ. Nirsevimab and other strategies for the prevention of RSV infection. *An Pediatr (Engl Ed)* 2023; **99**(4): 221-3.	Wrong publication type
Pfizer. A Study to Learn About the Safety and Immune Activity of RSVpreF in Children Who Are at High Risk of Getting RSV Disease. 2024. https://classic.clinicaltrials.gov/show/NCT05900154	Wrong population
Vivo Services limited. A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Immunogenicity and Efficacy of A Respiratory Syncytial Virus Vaccine (RSVpreF) in A Virus Challenge Model in H. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-003887-21	Wrong population
GlaxoSmithKline. Study of Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline's (GSK)Respiratory Syncytial Virus (RSV)Maternal Unadjuvanted Vaccine in Healthy Pregnant Women (Aged 18 to 40 Years) and Their Infants. 2020. https://classic.clinicaltrials.gov/show/NCT04126213	Wrong intervention

H.1.3 Quality assessment

The conducted SLR followed established SLR methodology, as described in the Cochrane Handbook[150] and the PRISMA statement[151]. By searching both Embase, MEDLINE, and Cochrane CENTRAL, the sensitivity of the searches was optimised, reducing the risk of missing potentially relevant studies. Additionally, ongoing or not yet published studies were identified through searches of clinicaltrials.gov and EUCTR.The conducted SLR followed established SLR methodology, as described in the Cochrane Handbook[150] and the PRISMA statement[151]. By searching both Embase, MEDLINE, and Cochrane CENTRAL, the sensitivity of the searches was optimised, reducing the risk of missing potentially relevant studies. Additionally, ongoing or not yet published studies were identified through searches of clinicaltrials.gov and EUCTR.

All screening of potentially relevant records was done by two reviewers in duplicate, minimising the risk of human error and thus the risk that potentially relevant studies were missed.

The SLR is reported in accordance with the PRISMA guidelines.

H.1.4 Unpublished data

All efficacy data included in this submission has been published, either in scientific journals or on clinicaltrials.gov

Some, detailed, safety data is not published, but is obtained from clinical study reports from the relevant trials, and as such is of high quality. The currently unpublished safety data is not planned to be published.

Appendix I. Literature searches for health-related quality of life

I.1 Objectives

A systematic literature review was conducted to identify published evidence of cost-utility evidence for the treatment of infants with RSV. As infants are not able to complete standard HRQoL instruments, only studies estimating utility decrements and/or QALD/Y loss were included in the review.

The research questions for this review were:

- What is the utility decrement / QALY loss associated with RSV infections and subsequent hospitalisations in infants entering their first RSV season.

I.2 Methods

This systematic review was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook, and in line with the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist.[151]

I.2.1 Information sources

The bibliographic databases searched are presented in Table 96. The search strategies for each bibliographic database are provided in Section I.2.2

Table 96. Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE ALL	PubMed	1946 to present	10.07.2024
Embase	Ovid	1980 to 2023 Week 05	10.07.2024

Conference proceedings were identified through the Embase search.

I.2.2 Search strategies

The search strategy was developed by creating three block searches: one for identifying studies within RSV, one for limiting studies to those including infants, and one for identifying studies estimating utility decrements or QALY loss.

The search block for RSV was built using both free-text terms and subject headings (MeSH for MEDLINE and Emtree for Embase).

The search block limiting the search to studies in infants is based on the filter published by the University of Pittsburgh (https://hsls.libguides.com/PubMed-search-filters/limiters).

The search block used to identify studies reporting utility or QALYs is based on the CADTH search filter to identify studies reporting health state utility values; however, as mentioned above, standard HRQoL instruments such as the SF-36 or EQ-5D are not appropriate for a patient population of infants, and thus the search filter was adapted to only identify studies specifically reporting utilities or QALYs.

I.2.2.1 Bibliographic database searches

The search strategies used, and the number of hits per search term are provided in Table 97 and Table 98.

Table 97. Search strategy - MEDLINE (Pubmed - 10/07/2024)

No.	Search term	Hits
#1	"respiratory syncytial virus, human"[Mesh]	4,454
#2	"respiratory syncytial virus infections"[Mesh]	9,335
#3	'respiratory syncytial virus*'[tiab] or 'rsv'[tiab]	23,275
#4	#2 OR #3 OR #4	23,990
#5	"Quality of Life"[mh] OR "Quality-Adjusted life years"[mh] OR (utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR weight[tiab])) OR disutility*[tiab]	471,025
#6	((child[mesh] OR adolescent[mesh] OR adult[mesh]) NOT infant[mesh])	9,044,417
#7	#4 AND #5 NOT #6	**168**

Table 98. Search strategy - MEDLINE (Embase - 10/07/2024)

No.	Search term	Hits
1	exp 'human respiratory syncytial virus'/	10,309
2	exp 'respiratory syncytial virus infection'/	9,053
3	('respiratory syncytial virus*' or rsv).ab,kw,ti.	29,802
4	1 or 2 or 3	34,426

5	exp "Quality of Life"/ OR exp "Quality-Adjusted life years"/ OR (utilit*.tw. AND (valu*.tw. OR measur*.tw. OR health.tw. OR life.tw. OR estimat*.tw. OR elicit*.tw. OR disease.tw. OR score*.tw. OR weight.tw.))	940,966
#6	(exp child/ or exp adolescent/ or exp adult/) not exp infant/	12,763,597
#7	(4 and 5) not 6	379

I.2.3 Systematic selection of studies

During primary screening, titles and abstracts of identified records were assessed against the population, intervention, comparator, outcomes and study design (PICOS) criteria, detailed in Table 99, to select those addressing the SLR eligibility criteria. This assessment was undertaken by two reviewers independently, using MS Excel. Electronic or paper copies of potentially relevant full papers meeting the SLR inclusion criteria were then obtained for secondary screening and assessed in detail for relevance to the eligibility criteria by two reviewers independently, and final selection of studies was made to inform the SLR. Where researchers disagreed regarding the inclusion or exclusion of a record at either primary or secondary screening, disagreements were discussed until a consensus was reached, potentially including a third reviewer.

Table 99. Inclusion and exclusion criteria used for assessment of studies

Criterion	Inclusion criteria	Exclusion
Population(s)	Infants or children under two years of age with RSV infection, regardless of risk factors	Studies only including children over two years of age or adults
Intervention/ Comparators	Any (including no treatment)	
Outcomes	Utility/disutility or QALY loss associated with RSV infections	
Study design	Randomised and non-randomised (comparative) clinical trials Non-comparative single-arm studies Observational studies	Case reports Animal studies
Publication types	Full-text peer reviewed publications Conference abstracts, posters and oral presentations	Non-systematic and systematic reviews Letters Editorials Commentaries Opinion pieces Press releases

The conducted searched identified 419 unique, potentially relevant studies. Of these, 403 were excluded at the title/abstract screening stage – leaving 16 potentially relevant studies for full text screening.

Of these 16 studies; 12 were excluded, leaving for studies reporting QALY loss or utility decrements for infants with RSV infections. An overview of the included studies is provided in Table 101 Overview of relevant studies . The studies excluded at the full-text stage are provided in Table 100. The flow of studies is visualised in a PRSIMA flowchart in .

Figure 23. PRISMA flowchart for HRQoL SLR

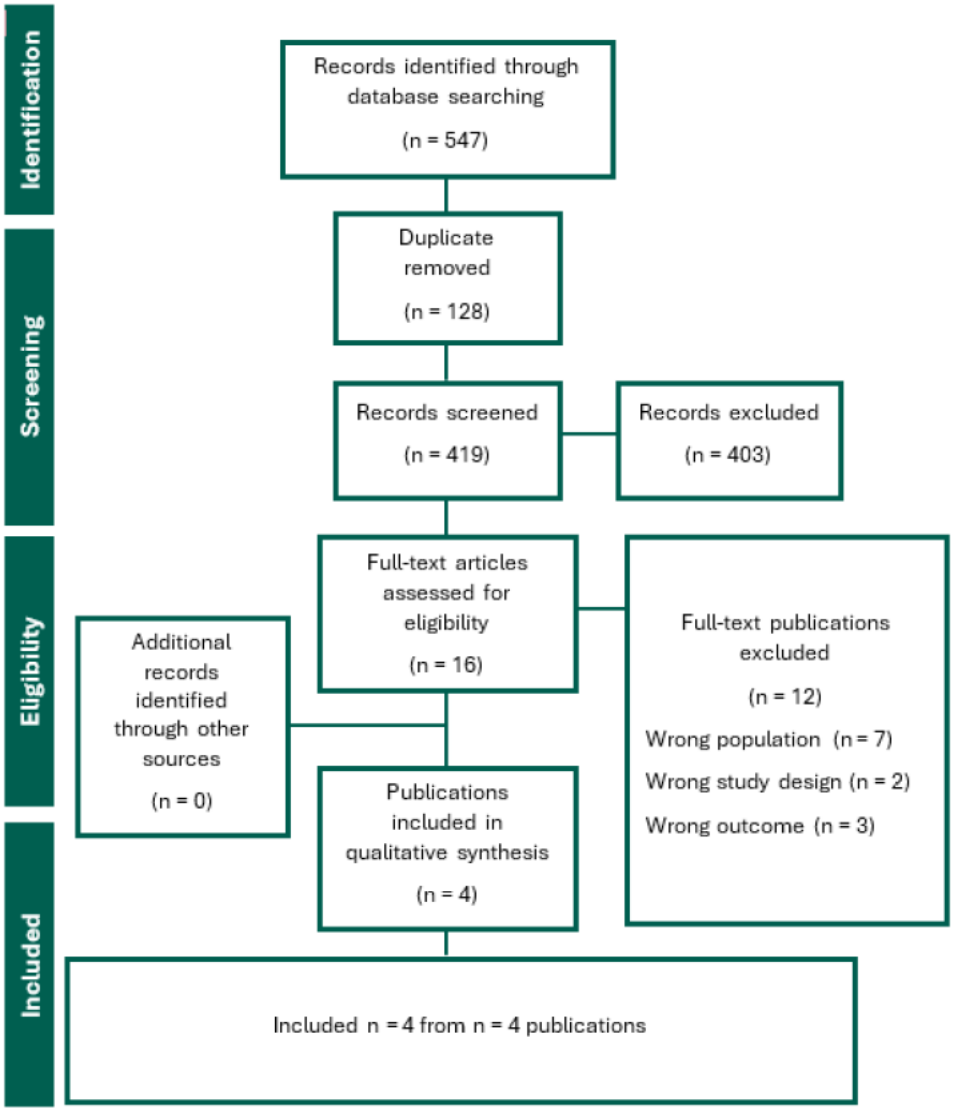


Table 100 Overview of excluded studies

Author	Year	Title	Reason for exclusion	DOI

L. Bont; M. Steijn; W. M. van Aalderen; J. L. Kimpen	2004	Impact of wheezing after respiratory syncytial virus infection on health-related quality of life	Wrong population	10.1097/01.inf.0000122604.32137.29
J. Díez-Domingo; E. G. Pérez-Yarza; J. A. Melero; M. Sánchez-Luna; M. D. Aguilar; A. J. Blasco; N. Alfaro; P. Lázaro	2014	Social, economic, and health impact of the respiratory syncytial virus: a systematic search	Wrong study design	10.1186/s12879-014-0544-x
E. Díez-Gandía; C. Gómez-Álvarez; M. López-Lacort; C. Muñoz-Quiles; I. Úbeda-Sansano; J. Díez-Domingo; A. Orrico-Sánchez	2021	The impact of childhood RSV infection on children's and parents' quality of life: a prospective multicenter study in Spain	Wrong outcome	10.1186/s12879-021-06629-z
J. Falco; T. Sweberg; P. Silver; J. Schneider	2014	Respiratory viruses causing acute respiratory failure in children: Outcomes and burden in the pediatric intensive care unit (PICU)	Wrong outcome	
E. L. Glaser; D. Hariharan; D. M. Bowser; R. M. Gervasio; K. R. Rowlands; L. Buckley; C. B. Nelson; D. S. Shepard	2022	Impact of Respiratory Syncytial Virus on Child, Caregiver, and Family Quality of Life in the United States: Systematic Literature Review and Analysis	Wrong study design	10.1093/infdis/jiac183
D. Hariharan; V. S. S. Kumar; E. L. Glaser; W. H. Crown; Z. A. Wolf; K. A. Fisher; C. T. Wood; W. F. Malcolm; C. B. Nelson; D. S. Shepard	2023	Quality of life burden on United States infants and caregivers due to lower respiratory tract infection and adjusting for selective testing: Pilot prospective observational study	Wrong population	
P. E. Heikkila; M. H. Ruotsalainen; M. O. Korppi; K. S. Backman	2020	Long-term health-related quality-of-life data in subjects with a history of	Wrong population	

		wheezing in early childhood		
A. T. Spuijbroek; R. Oostenbrink; J. M. Landgraf; E. Rietveld; A. de Goede-Bolder; E. F. van Beeck; M. van Baar; H. Raat; H. A. Moll	2011	Health-related quality of life in preschool children in five health conditions	Wrong population	10.1007/s11136-010-9806-2
I. Trautmannsberger; S. Bösl; C. Tischer; J. Kostenzer; S. Mader; L. J. I. Zimmermann; Q. F. S. G. The Res	2023	ResQ Family: Respiratory Syncytial Virus (RSV) Infection in Infants and Quality of Life of Families-Study Protocol of a Multi-Country Family Cohort Study	Wrong population	10.3390/ijerph20115917
I. Trautmannsberger; B. Plagg; I. Adamek; S. Mader; D. de Luca; S. Esposito; S. A. Silfverdal; L. J. I. Zimmermann; C. Tischer	2024	The Multifaceted Burden of Respiratory Syncytial Virus (RSV) Infections in Young Children on the Family: A European Study	Wrong population	
J. G. Wildenbeest; R. P. Zuurbier; K. Korsten; M. A. van Houten; M. N. Billard; N. Derksen-Lazet; M. D. Snape; S. B. Drysdale; H. Robinson; A. J. Pollard; T. Heikkinen; S. Cunningham; A. Leach; F. Martinon-Torres; C. R. T. Sanchez; A. Gomez-Carballa; L. J. Bont; H. Nair; H. Campbell; P. Openshaw; P. Beutels; E. Molero; A. Meijer; E. Sanders; T. K. Fischer; M. van den Berge; C. Giaquinto; M. Esser; C. Knirsch; S. Gallichan; J. Aerssens; B. Rosen	2020	Respiratory syncytial virus consortium in Europe (RESCEU) birth cohort study: Defining the burden of infant respiratory syncytial virus disease in Europe	Wrong outcome	
A. Wrotek; O. Wrotek; T. Jackowska	2023	The Estimate of Parental Quality of Life Loss Due to Respiratory Syncytial Virus	Wrong population	10.3390/diseases11040126

(RSV)
Hospitalization

Table 101 Overview of relevant studies for the SLR

Study ID	Study design	Population	Results
Hodgson 2020[127]Hodgson 2020[127]	Questionnaire study using a regression model to estimate QALY loss associated with RSV episodes based on EQ-5D	Children <5 with RSV compared to a control group of <5 year olds that did not seek health care	**Estimated QALY loss per healthcare-seeking RSV episode in children less than 5 years old:** $3.8323*10^{-3}$ (95% CI: 0.429-$12.766*10^{-3}$) **Estimated QALY loss per non-healthcare-seeking RSV episode in children less than 5 years old:** $3.024*10^{-3}$ (95% CI: 0.329-$10.098*10^{-3}$)
Mao 2023[125]Mao 2023[125]	Prospective study, examining the quality-of-life impact and healthcare costs associated with RSV episodes, using a modified EQ-5D with a visual analogue scale	Healthy term-born infants	**Estimated QALD loss per RSV episode:** 1.9 (1.7 to 2.1) – the QALD loss was independent of medical attendance
Ren 2023[152]Ren 2023[152]	Prospective case series study examining HRQoL loss associated with RSV infections using the PedsQL Infant Scale. The PedsQL scores were then mapped to EQ-5D-Y to estimate QALY loss by multiplying the utility loss with the reported duration of RSV illness	Inpatients, under 5 years of age and having an acute onset of symptoms of respiratory infection	**Mean QALY loss per RSV hospitalisation in 0-11 months olds:** $9.7*10^{-3}$ (95% CI: 8.3 to $11.1*10^{-3}$) **Median QALY loss per RSV hospitalisation in 0-11 months olds:** $7.9*10^{-3}$ (95% CI: 5.3 to $11.3*10^{-3}$)
Wrotek 2023[153]Wrotek 2023[153]	Prospective study on quality of life of children under 2 years of age, assessed by the	Children under 2 years of age hospitalized due to a laboratory-	**Median QALY loss attributable to RSV** $6.03*10^{-3}$ (95%CI: 4.38 to $8.48*10^{-3}$)

	caregivers with a visual analogue scale	confirmed RSV infection.

I.2.4 Unpublished data

Not relevant

Appendix J. Literature searches for input to the health economic model

No SLR has been carried out for this assessment. Instead, a targeted literature review was performed to identify Danish-specific information on costs, RSV epidemiology and seasonality, and HRQoL as well as support evidence provided by data from Danish registries on risk of intensive care observation or treatment and the risk of mechanical ventilation. A pragmatic search of MEDLINE to identify publications on epidemiology and complications of RSV in Danish infants was conducted (summarised below); additionally, websites such as ssi.dk were searched for relevant input.

Pragmatic search:

The search strategy employed to identify studies examining RSV in Danish infants is presented in Table 102

Table 102. Search strategy - Input to the health economic model - MEDLINE (06-09-2024)

No.	Search term	Hits
#1	"respiratory syncytial virus, human"[Mesh]	4,555
#2	"respiratory syncytial virus infections"[Mesh]	9,498
#3	'respiratory syncytial virus*'[tiab] or 'rsv'[tiab]	23,598
#4	#1 OR #2 OR #3	24,318
#6	'infant'[Mesh]	1,285,646
#7	'infant'[All fields]	1,420,947
#8	#6 OR #7	1,420,947
#9	#4 AND #8	9,715

#10	'denmark'[Mesh]	57,714
#11	'denmark'[All fields]	313,322
#12	#10 OR #11	313,322
#13	#9 AND #12	**92**

The 92 identified records were screened at the title/abstract level by a single reviewer. Full texts of potentially eligible records were then screened by the same reviewer to find finally eligible records. The records were screened to determine if they contained information that could inform the health economic model.

Seventy-eight records were excluded at the title/abstract level, leaving 14 potentially eligible records for full-text screening. Of these, X were found to contain information that could potentially inform the health economic model. shows the potentially relevant studies, whether they are informing the health economic model, and a rationale for inclusion/exclusion. Table 103 shows the studies excluded at the full-text stage and the reason for exclusion.

Study	Description	Included in model?	Rationale
Jepsen et al. 2018[5]	Examines incidence of RSV-hospitalisations in Danish children < 5 years old between 2010-2015.	No	While the study contains data that could be included in the model, more up to date is available.
Jensen et al. 2021[43]	Examines incidence of RSV-hospitalisations for children born in Denmark between 2010-2016.	No	While the study contains tata that could be included in the model, more recent data is available. Additionally, data is only presented for 0-12 months as an overall risk and would require additional assumptions to include.
Reeves et al. 2020[154]	Examines incidence of RSV-hospitalisations in 7 European countries, including Denmark, in children < 5 years old between 2001 and 2017.	No	While the study contains data that could be included in the model, more up to date is available.
Del Riccio et al. 2023[155]	Estimates hospitalisation rates for children < 5 years old in European countries, including	No	While the study contains data that could be included in the model, more up to date is available.

	Denmark. Estimates are based on data from 2006 to 2018		
Nygaard et al. 2023[116]	Estimates hospitalisation and mechanical ventilation rates for Danish children < 5 years old for the 2016/2017 to 2019/2020 and 2021/2022 seasons	Yes	The study is used to inform rates of mechanical ventilation. The study could also be used to inform hospitalisation rates; however, more up to data is available. Additionally, the study estimates lower hospitalisation rates than other published studies. An option to use hospitalisation rates from the study has been added in the model.
Johannesen et al. 2022[156]	Examines incidence of RSV-hospitalisations in 6 European countries, including Denmark, in children < 5 years old between 2016 and 2018.		While the study contains data that could be included in the model, more up to date is available.

Table 103. Studies excluded after full text screening (literature for the health economic model)

Reference	Reason for exclusion
Wang, X., et al. (2022). "Respiratory Syncytial Virus-Associated Hospital Admissions and Bed Days in Children <5 Years of Age in 7 European Countries." J Infect Dis **226**(Suppl 1): S22-S28.	Does not present data in a way that allows for inclusion in model
Haerskjold A, Kristensen K, Kamper-Jorgensen M, Nybo Andersen AM, Ravn H, Graff Stensballe L. Risk Factors for Hospitalization for Respiratory Syncytial Virus Infection: A Population-based Cohort Study of Danish Children. Pediatr Infect Dis J 2016; 35(1): 61-5.	Only presents hospitalisation risk for 0–24-month-olds as overall risk
Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. *Clin Infect Dis* 2008; **46**(8): 1165-71.	Does not present data for RSV hospitalisation alone, only as related to invasive pneumococcal disease
Stensballe LG. An epidemiological study of respiratory syncytial virus associated hospitalizations in Denmark. *Respir Res* 2002; **3 Suppl 1**(Suppl 1): S34-9.	Protocol, does not present results
Kristensen K, Dahm T, Frederiksen PS, et al. Epidemiology of respiratory syncytial virus infection requiring hospitalization in East Denmark. Pediatr Infect Dis J 1998; 17(11): 996-1000.	Only included children <6 month from East Denmark

Nygaard U, Nielsen J, Nielsen JSA, et al. The magnitude and severity of paediatric RSV infections in 2022-2023: A Danish nationwide cohort study. *Acta Paediatr* 2023; **112**(10): 2199-201.	Compares post- and pre-covid seasons, but does not present overall risk.
Getaneh AM, Li X, Mao Z, et al. Cost-effectiveness of monoclonal antibody and maternal immunization against respiratory syncytial virus (RSV) in infants: Evaluation for six European countries. *Vaccine* 2023; **41**(9): 1623-31.	Relies on data published in Johannesen et al. 2022
Munkstrup C, Lomholt FK, Emborg HD, et al. Early and intense epidemic of respiratory syncytial virus (RSV) in Denmark, August to December 2022. *Euro Surveill* 2023; **28**(1).	Discusses 2021/2022 season, but does not provide estimates of hospitalisation rates in infants

Epidemiology:

Data from the Danish RSV dashboard was used to inform the incidence of RSV cases and to support the decision of setting season length to 4 months in the health economic model.

Costs:

Cost inputs of the health economic model have been collected from Danish DRG tariffs, Medicinpriser.dk, DMC's unit cost catalogue for the following:

- Medicine costs
- Disease management costs (RSV-related health events provided by Danish RWE data)
- Costs associated with RSV specific complications (per patient risk sourced from Li et al. 2022)[87].
  Patient time and transportation costs: linked to the RSV-related events/incidence provided by Danish RWE data (inpatient and outpatient visits) and linked to RSV-specific complications (Li et al. 2022)[87].

Health-related quality of life:

Due to the challenges in collecting HRQoL data on infant populations[157], data used to inform disutilities for RSV-related adverse events was derived from well-established studies on the estimation of infant's HRQoL (see section Due to the challenges in collecting HRQoL data on infant populations[157], data used to inform disutilities for RSV-related adverse events was derived from well-established studies on the estimation of infant's HRQoL (see section 10.2).

Reported below is the rationale used to convert the QALD presented in the Mao Z. et al. (2022) to the disutilities used in the model at the occurrence of an RSV-related adverse event.

Based on the quality-adjusted life day (QALD) loss outcomes reported from Mao Z. et al. (Table 3), we identified RSV-related QALY disutilities per RSV-related adverse event. Specifically, a QALD loss of 3.7 from the pooled infant population corresponded to a QALY loss of 0.0101 in the model. Open hospitalisation "åben indlæggelse" included in the model, with QALY loss of 0.0038 was calculated starting from a QALD of 1.3 reported in the study. Finally primary care and paediatric department visits, with modelled QALY loss of 0.0063 were adapted from QALD losses of 2.3[125].[125].

Appendix K. Safety data and patient disposition from MEDLEY

Safety data from MEDLEY (season 1), comparing the safety profile of nirsevimab to that of palivizumab is shown in Table 104. All observed serious adverse events are provided in Table 80.

Table 104. Safety data – MEDLEY (Season 1)

	Nirsevimab (n = 614)	Palivizumab (n =304)
Number of adverse events, n	1911	977
Number and proportion of patients with ≥1 adverse events, n (%)	444 (72.3%)	215 (70.7%)
Number of serious adverse events*, n	114	59
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	80 (13.0%)	38 (12.5%)
Number of CTCAE grade ≥ 3 events, n	Not available	Not available

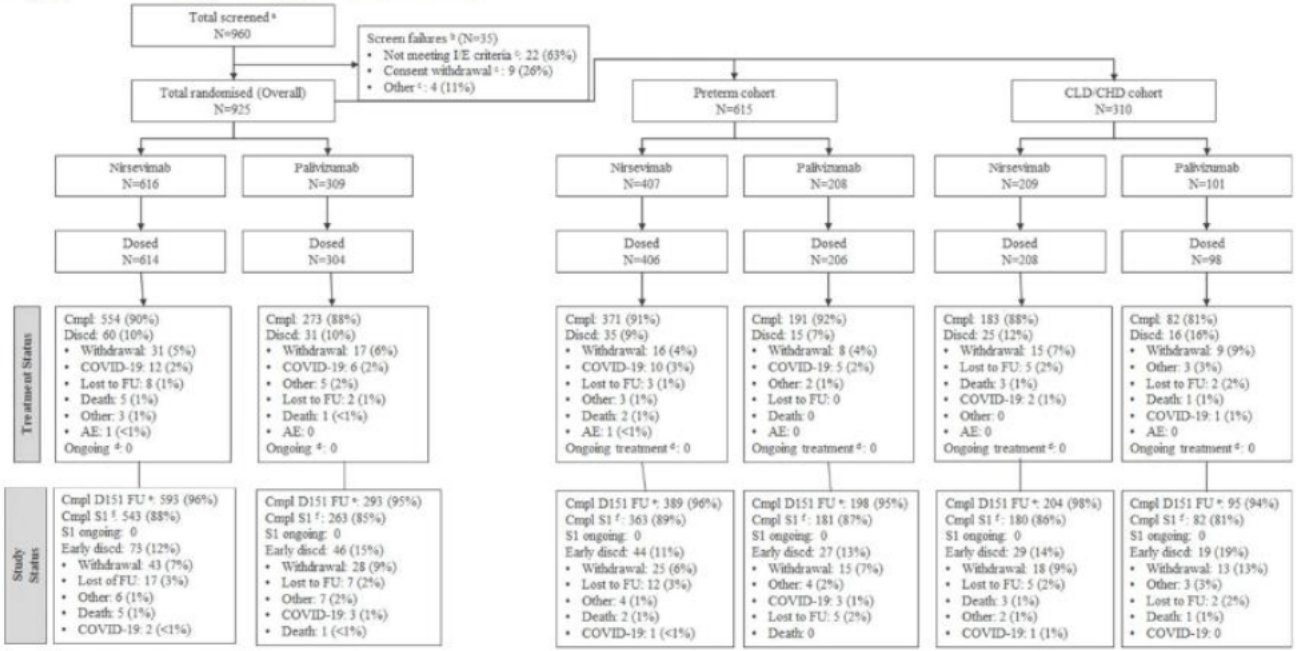
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	50 (8.1%)	25 (8.2%)
Number of adverse reactions (Treatment-related), n	6	10
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	6 (2.0%)	10 (1.6%)

Source: Clinical study report[158]

The patient disposition for infants included in season 1 of the MEDLEY trial is shown in Figure 24.

Figure 24. Patient disposition in MEDLEY (season 1)

Figure 2 Subject Disposition (Season 1)



[a] Subjects signed the informed consent.
[b] Denominator is the number of subjects screened.
[c] Denominator is the number of screen failures.
[d] Subjects who did not receive Day 121 dose up to the data cut-off date and did not have end of treatment page.
[e] Numerator includes subjects whose study status was ongoing on Season 1 Day 151.
[f] Completed Season 1 = completed Day 361 FU.

AE = adverse event; CHD = congenital heart disease; CLD = chronic lung disease; Cmpl = completed; COVID-19 = coronavirus disease 2019; D 151 = Day 151; Discd = discontinued; FU = follow-up; I/E = inclusion/exclusion; S1 = Season 1.
Source: Table 14.1.1.1.

Appendix L. Resource use based on RSV-related Health Events

L.1.1 Medical resource use

The burden of RSV is captured in the model by the risk of RSV MA-LRTI events treated as inpatient hospitalizations, intensive care or observation visits, MV, outpatient hospitalizations, pediatric emergency visits, and PC visits etc. The per-patient risk of each health event is stratified by the infant's age at the time of infection. Infant age is defined by month from 0 to 11 months and then by year for infants aged 12 to 24 months and 25 to 36 months (the same monthly risk is applied to infants aged 12 to 24 months and those aged 25 to 36 months). Data is based on Danish registry data. No data beyond 1 year of age was extracted from the registry.

The base-case analysis includes inpatient hospitalizations, intensive care or observation admissions, MV, pediatric emergency visits, and PC visits. To account for the uncertainty in the incidence rates of health events, the lowest and highest credible values based on alternative sources or the 95% confidence intervals reported in the original studies were used when available.

L.1.1.1 Inpatient hospitalisation

Table 105. RSV-related health events – hospitalisations

Age at time of infection	Overall population	Palivizumab eligible infants	Preterm infants	Term infants
0 months	4.12%	28.10%	7.08%	4.00%
1 months	9.28%	63.28%	15.94%	9.01%
2 months	7.39%	50.37%	12.69%	7.17%
3 months	4.20%	28.63%	7.21%	4.08%
4 months	2.84%	19.33%	4.87%	2.75%
5 months	2.37%	16.15%	4.07%	2.30%
6 months	1.26%	8.61%	2.17%	1.23%
7 months	1.11%	7.53%	1.90%	1.07%
8 months	0.94%	6.41%	1.62%	0.91%
9 months	0.75%	5.09%	1.28%	0.72%

10 months	0.53%	3.64%	0.92%	0.52%
11 months	0.84%	5.76%	1.45%	0.82%
12 - 24 months				
25 - 36 months				

Source: Danish Registry data

L.1.1.2 Intensive care or observation

Table 106. RSV-related health events –Intensive care or observation

Age at time of infection	Overall population	Palivizumab eligible infants	Preterm infants	Term infants
0 months	12.41%	19.48%	24.15%	12.08%
1 months	9.02%	14.16%	17.56%	8.78%
2 months	6.62%	10.39%	12.88%	6.44%
3 months	5.04%	6.33%	5.89%	5.02%
4 months	4.51%	5.65%	5.26%	4.48%
5 months	4.75%	5.96%	5.54%	4.72%
6 months	5.31%	5.92%	5.61%	5.30%
7 months	5.47%	6.10%	5.78%	5.46%
8 months	5.81%	6.48%	6.14%	5.80%
9 months	7.05%	7.86%	7.45%	7.04%
10 months	6.12%	6.83%	6.47%	6.11%
11 months	6.55%	7.31%	6.92%	6.54%
12 - 24 months				
25 - 36 months				

Source: Danish Registry data

L.1.1.3 Mechanical ventilation

Table 107. RSV-related health events – MV

Age at time of infection	Overall population	Palivizumab eligible infants	Preterm infants	Term infants
0 months	1.72%	3.12%	4.22%	1.65%
1 months	1.72%	3.12%	4.22%	1.65%
2 months	1.72%	3.12%	4.22%	1.65%
3 months	0.50%	1.18%	1.42%	0.47%
4 months	0.50%	1.18%	1.42%	0.47%
5 months	0.50%	1.18%	1.42%	0.47%
6 months	1.09%	2.61%	2.61%	1.05%
7 months	1.09%	2.61%	2.61%	1.05%
8 months	1.09%	2.61%	2.61%	1.05%
9 months	1.09%	2.61%	2.61%	1.05%
10 months	1.09%	2.61%	2.61%	1.05%
11 months	1.09%	2.61%	2.61%	1.05%
12 - 24 months				
25 - 36 months				

Source: Nygaard et al 2023 (post-covid)[116])[116]

L.1.1.4 Pediatric emergency admission

Table 108. RSV-related health events – pediatric emergency admission

Age at time of infection	Overall population	Palivizumab eligible infants	Preterm infants	Term infants
0 months	1.96%	1.96%	1.96%	1.96%
1 months	6.42%	6.42%	6.42%	6.42%
2 months	7.24%	7.24%	7.24%	7.24%

3 months	10.52%	10.52%	10.52%	10.52%
4 months	11.60%	11.60%	11.60%	11.60%
5 months	7.13%	7.13%	7.13%	7.13%
6 months	8.18%	8.18%	8.18%	8.18%
7 months	5.61%	5.61%	5.61%	5.61%
8 months	5.56%	5.56%	5.56%	5.56%
9 months	5.56%	5.56%	5.56%	5.56%
10 months	4.04%	4.04%	4.04%	4.04%
11 months	5.56%	5.56%	5.56%	5.56%
12 - 24 months				
25 - 36 months				

Source: Danish Registry data

L.1.1.5 Primary care visit

Table 109. RSV-related health events – PC visit

Age at time of infection	Overall population	Palivizumab eligible infants	Preterm infants	Term infants
0 months	20.61%	14.92%	14.92%	14.92%
1 months	46.42%	33.60%	33.60%	33.60%
2 months	36.95%	26.75%	26.75%	26.75%
3 months	21.01%	15.21%	15.21%	15.21%
4 months	14.18%	10.27%	10.27%	10.27%
5 months	11.85%	8.58%	8.58%	8.58%
6 months	15.80%	11.44%	11.44%	11.44%
7 months	13.82%	10.00%	10.00%	10.00%
8 months	11.76%	8.51%	8.51%	8.51%

9 months	9.33%	6.76%	6.76%	6.76%
10 months	6.68%	4.83%	4.83%	4.83%
11 months	10.56%	7.64%	7.64%	7.64%
12 - 24 months				
25 - 36 months				

Source: Danish Registry data

Appendix M. PSA results by subgroup

PSA results presented as Scatter plots and CEAC curves are presented below by each subgroup: Palivizumab eligible population, Preterm infant population, and Term infant population.

M.1 Palivizumab eligible population

M.1.1 Nirsevimab vs Maternal immunisation

M.1.2 Nirsevimab vs SoC

M.2 Preterm infant population

M.2.1 Nirsevimab vs Maternal immunisation

M.2.2 Nirsevimab vs SoC

M.3 Term infant population

M.3.1 Nirsevimab vs Maternal immunisation

M.3.2 Nirsevimab vs SoC

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk / www.medicinraadet.dk