Coversheet on evidence assessment by ATAGI using the GRADE framework for Arexvy (GSK) recombinant respiratory syncytial virus pre-fusion F protein vaccine (RSVPreF3) adjuvanted with AS01E in adults aged 50–59 years with medical risk factors for severe disease

Background

- Respiratory syncytial virus (RSV) infection is an increasingly recognised cause of significant hospitalisation, morbidity and mortality in older adults and in people with comorbid conditions.
- RSV vaccines targeting the prefusion F protein are being investigated for their efficacy in preventing infection and severe disease.

Research questions

1. Should Arexvy (GSK; recombinant respiratory syncytial virus pre-fusion F protein vaccine [RSVPreF3] adjuvanted with AS01E) be recommended for adults aged 50–59 years with medical risk factors for severe disease to prevent respiratory syncytial virus disease?

Table 1: Population, Intervention, Comparator, Outcomes (PICO)

Population	Aged 50–59 years with medical risk factors for severe disease*
Intervention	Arexvy (GSK) adjuvanted RSV vaccine
Comparator	Placebo
Outcomes	*Critical* • RSV (laboratory confirmed) lower respiratory tract illness/disease (LRTI/LRTD) • Severe RSV (laboratory confirmed) LRTI/LRTD • Serious adverse events (SAEs) • RSV (laboratory confirmed) medically attended LRTI/LRTD • Hospitalisation for RSV respiratory illness • Death due to RSV respiratory illness *Important* • RSV A/B LRTD/LRTI • RSV (laboratory confirmed) acute respiratory infection • Solicited systemic adverse events • Solicited local adverse events • RSV A/B neutralising antibodies geometric mean fold rise/ mean geometric increases • RSV A/B seroresponse rate^

* Medical risk factors include cardiac disease; chronic respiratory conditions; immunocompromising conditions; chronic metabolic disorders, including diabetes; chronic kidney disease (stage 4 or 5); chronic neurological conditions; obesity

^ Seroresponse rate is defined as the percentage of participants with a 4-fold or greater increase in neutralisation titers from pre- to 1-month post-vaccination/12 months post vaccination.

Literature search

A literature search was undertaken in the following databases: Medline, Embase and Cochrane CENTRAL on 6 November 2024 to identify studies assessing efficacy and/or safety outcomes of the RSVPreF3 (Arexvy) vaccine in adults. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- *Study design*: Randomised controlled trial (RCT), observational study, meta-analysis
- *Population*: Age 50–59 years with medical risk factors for severe disease
- *Intervention*: RSV vaccine
- *Comparator*: Placebo
- *Outcomes*: Effectiveness, efficacy, safety

Rationale for the inclusion criteria and PICO of the GRADE assessment are presented in Table 2.

A total of 222 citations were screened for review. Of these, one randomised controlled trial (Ferguson et al. 2024) met the above pre-defined inclusion criteria and was included in GRADE analysis.

Arexvy RSVPreF3 compared with placebo

Inclusion criteria and rationale

Table 2: Rationale for PICO and inclusion criteria

PICO	Rationale
Study type: RCT, observational study, effectiveness studies	All study types included, expecting little evidence available in this population.
Population: Age 50–59 years with medical risk factors	Extended age registration for this vaccine by the Therapeutic Goods Administration
	Medical risk factors include cardiac disease; chronic respiratory conditions; immunocompromising conditions; chronic metabolic disorders, including diabetes; chronic kidney disease (stage 4 or 5); chronic neurological conditions; obesity. List of risk factors as per the Australian Immunisation Handbook
Intervention: Arexvy (GSK) adjuvanted RSV vaccine	Current formulation in terms of dosage and included antigens and presence/absence of adjuvants.
Comparator: Placebo / no vaccine	There are no current comparator vaccines.
Outcomes	Only immunogenicity and safety outcome data were available in the proposed population. As such, the included outcomes were: *Critical* • Serious Adverse Events (SAEs) and adverse events of special interest (AESI) *Important* • Solicited systemic adverse events • Solicited local adverse events

	• RSV A/B neutralising antibodies geometric mean fold rise/ mean geometric increases at 30 days and 12 months post vaccination • RSV A/B seroresponse rate^ at 30 days and 12 months post vaccination The following two immunogenicity outcomes were not included in the GRADE assessment due to low sample size • Frequencies of RSVPreF3-specific CD4+ T cells expressing 2 or more activation markers • Percentage of participants with 4-fold increase in RSVPreF3-specific CD4+ T cells expressing 2 or more activation markers 30 days post vaccination
	As per the general framework for outcomes included in the GRADE assessment, additional immunogenicity outcomes were included due to limited efficacy and effectiveness data in this population. Efficacy and effectiveness data in other populations is referenced in the Evidence to Decision Framework to supplement the assessment.
	Ranking of importance discussed in many iterations with portfolio leads and/ ATAGI full panel.
	General framework (depending on outcomes measured in studies available): *Critical* • RSV (laboratory confirmed) lower respiratory tract illness/disease (LRTI/LRTD) ▪ Severe RSV (laboratory confirmed) lower respiratory tract illness/disease (LRTI/LRTD) • RSV (laboratory confirmed) medically attended LRTI/LRTD • Hospitalisation for RSV respiratory illness • Death due to RSV respiratory illness • Serious adverse events (SAEs) and adverse events of special interest (AESI) *Important* • RSV A/B LRTD/LRTI • RSV (laboratory confirmed) Acute respiratory infection • Systemic adverse events • Local adverse events • Immunogenicity outcomes Note: Some outcomes may be missing in GRADE projects due to no data from available studies. Extra outcomes added due to relevance.

Risk of bias assessment

Risk of bias (RoB) assessment was carried out on the included study by two assessors using ROB 2.0. Details of the RoB assessment are presented in Appendix B.

Appendix A: search strategy

EMBASE: RSV vaccines – GSK older adults – FINAL (as at 06.11.24) **Notes: No age, language or date limits applied. Previous search was conducted on 27.06.23. This search uses the same strategy but is not date limited.** Database: Embase <1974 to 2024 November 04> Search Strategy: --- 1 exp Human respiratory syncytial virus/ (10898) 2 exp respiratory syncytial virus infection/ (9580) 3 (respiratory adj2 syncytial).tw. (22526) 4 rsv.tw. (22260) 5 1 or 2 or 3 or 4 (35482) 6 exp Immunization/ (406985) 7 exp vaccine/ (445817) 8 (immuni$ or vaccin$).tw. (860903) 9 6 or 7 or 8 (1022057) 10 5 and 9 (9145) 11 exp respiratory syncytial virus vaccine/ (2648) 12 10 or 11 (9485) 13 (GlaxoSmithKline$ or GSK$).tw. (50023) 14 Arexvy$.tw. (49) 15 AReSVi$.tw. (8) 16 ("RSV 007$" or RSV-007$ or RSV007$).tw. (2) 17 ("RSV pre F3$" or RSV-pre-F3$ or RSVpreF3$).tw. (61)	**MEDLINE: RSV vaccines – GSK older adults – FINAL (as at 06.11.24)** **Notes: No age, language or date limits applied. Previous search was conducted on 27.06.23. This search uses the same strategy but is not date limited.** Database: Ovid MEDLINE® All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 exp Respiratory Syncytial Virus, Human/ (4638) 2 exp Respiratory Syncytial Virus Infections/ (9661) 3 (respiratory adj syncytial).tw. (18221) 4 rsv.tw. (16576) 5 1 or 2 or 3 or 4 (24528) 6 exp Immunization/ (220003) 7 exp Immunization Programs/ (16709) 8 exp Vaccines/ (292966) 9 (immuni$ or vaccin$).tw. (723876) 10 6 or 7 or 8 or 9 (827617) 11 5 and 10 (5721) 12 exp Respiratory Syncytial Virus Vaccines/ (1138) 13 11 or 12 (5752) 14 (GlaxoSmithKline$ or GSK$).tw. (26692) 15 Arexvy$.tw. (27) 16 AReSVi$.tw. (4)	**Cochrane Library Central Register of Controlled Trials (CENTRAL), Issue 10 of 12, October 2024: RSV vaccines – GSK older adults – FINAL (as at 06.11.24)** **Notes: No age, language or date limits applied. Previous search was conducted on 27.06.23. This search uses the same strategy but is not date limited.** ID Search Hits #1 MeSH descriptor: [Respiratory Syncytial Virus, Human] explode all trees 162 #2 MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees 558 #3 ("respiratory syncytial"):ti,ab,kw 1374 #4 rsv:ti,ab,kw 1256 #5 #1 OR #2 OR #3 OR #4 1651 #6 MeSH descriptor: [Immunization] explode all trees 7490 #7 MeSH descriptor: [Immunization Programs] explode all trees 349 #8 MeSH descriptor: [Vaccines] explode all trees 17671 #9 (immuni* OR vaccin*):ti,ab,kw 43129 #10 #6 OR #7 OR #8 OR #9 43339 #11 #5 AND #10 579 #12 MeSH descriptor: [Respiratory Syncytial Virus Vaccines] explode all trees 104 #13 #11 OR #12 579 #14 (GlaxoSmithKline* OR GSK*):ti,ab,kw 5301 #15 Arexvy*:ti,ab,kw 7

18 ("RSVPreF3 OA" or "RSVPreF3-OA" or "RSVPreF3OA").tw. (35) 19 AS01$.tw. (812) 20 NCT04886596$.tw. (13) 21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (50827) 22 12 and 21 (141) 23 exp vaccine immunogenicity/ (8361) 24 immunogen$.tw. (132337) 25 exp antibody production/ (64372) 26 exp antibody response/ (67973) 27 (antibod$ adj3 (respons$ or form$)).tw. (85743) 28 (immun$ adj3 (respon$ or protect$)).tw. (549532) 29 exp virus antibody/ (113208) 30 exp neutralizing antibody/ (57499) 31 exp drug efficacy/ (1068250) 32 efficac$.tw. (1777042) 33 effective$.tw. (3650795) 34 exp safety/ (599626) 35 exp postmarketing surveillance/ (40303) 36 exp drug surveillance program/ (26989) 37 exp adverse drug reaction/ (678545) 38 (adverse adj3 (effect$ or event$)).tw. (813716) 39 (safe or safety or aefi or aesi).tw. (1720323) 40 exp mortality/ (1485391) 41 exp death/ (2161182) 42 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (3368285) 43 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (10588079) 44 22 and 43 (121)	17 ("RSV 007$" or RSV-007$ or RSV007$).tw. (0) 18 ("RSV pre F3$" or RSV-pre-F3$ or RSVpreF3$).tw. (37) 19 ("RSVPreF3 OA" or "RSVPreF3-OA" or "RSVPreF3OA").tw. (16) 20 AS01$.tw. (574) 21 NCT04886596$.tw. (5) 22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (27251) 23 13 and 22 (68) 24 exp Immunogenicity, Vaccine/ (3757) 25 immunogen$.tw. (99797) 26 exp Antibody Formation/ (64069) 27 (antibod$ adj3 (respons$ or form$)).tw. (72828) 28 (immun$ adj3 (respon$ or protect$)).tw. (422011) 29 exp Antibodies, Viral/ (127679) 30 exp Antibodies, Neutralizing/ (20704) 31 exp Treatment Outcome/ (1312427) 32 exp Vaccine Efficacy/ (1254) 33 efficac$.tw. (1224410) 34 effective$.tw. (2834810) 35 exp Safety/ (90858) 36 exp Safety-Based Drug Withdrawals/ (422) 37 exp Product Surveillance, Postmarketing/ (19263) 38 exp Drug Evaluation/ (42086) 39 exp Population Surveillance/ (75178) 40 exp Adverse Drug Reaction Reporting Systems/ (9455) 41 (adverse adj3 (effect$ or event$)).tw. (518230) 42 (safe or safety or aefi or aesi).tw. (1144756) 43 exp Mortality/ (434048)	#16 AReSVi*:ti,ab,kw 6 #17 ((RSV NEXT 007*) OR RSV-007* OR RSV007*):ti,ab,kw 0 #18 ((RSV NEXT pre F3*) OR RSV-pre-F3* OR RSVpreF3*):ti,ab,kw 82 #19 ((RSV NEXT PReF30A) OR RSVPreF3OA):ti,ab,kw 1 #20 AS01*:ti,ab,kw309 #21 NCT04886596*:ti,ab,kw 18 #22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 5583 #23 #13 AND #22 108 #24 MeSH descriptor: [Immunogenicity, Vaccine] explode all trees 974 #25 immunogen*:ti,ab,kw 18502 #26 MeSH descriptor: [Antibody Formation] explode all trees 1244 #27 (antibod* NEAR/3 (respons* OR form*)):ti,ab,kw 6344 #28 (immun* NEAR/3 (respon* OR protect*)):ti,ab,kw 20198 #29 MeSH descriptor: [Antibodies, Viral] explode all trees 5320 #30 MeSH descriptor: [Antibodies, Neutralizing] explode all trees 1114 #31 MeSH descriptor: [Treatment Outcome] explode all trees 206471 #32 MeSH descriptor: [Vaccine Efficacy] explode all trees 100 #33 efficac*:ti,ab,kw 478578 #34 effective*:ti,ab,kw 457727 #35 MeSH descriptor: [Safety] explode all trees 5161 #36 MeSH descriptor: [Safety-Based Drug Withdrawals] explode all trees 12

	44 exp Death/ (169772) 45 (mortalit$ or death$ or fatal$ or case-fatal$ or lethal$ or died).tw. (2344623) 46 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (7823835) 47 23 and 46 (64)	#37 MeSH descriptor: [Product Surveillance, Postmarketing] explode all trees 571 #38 MeSH descriptor: [Drug Evaluation] explode all trees 6560 #39 MeSH descriptor: [Population Surveillance] explode all trees 911 #40 MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees 186 #41 (adverse NEAR/3 (effect* OR event*)):ti,ab,kw 355382 #42 (safe OR safety OR aefi OR aesi):ti,ab,kw 367925 #43 MeSH descriptor: [Mortality] explode all trees 18997 #44 MeSH descriptor: [Death] explode all trees 3582 #45 (mortalit* OR death* OR fatal* OR case-fatal* OR lethal* or died) 205599 #46 #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 1159001 #47 #23 AND #46 108

Appendix B: Risk of Bias

Table 2: Risk of bias assessment for randomised controlled trials using ROB 2.0

Study	Outcome	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Ferguson et al. 2024	Immunogenicity	Low	Low	Low	Low	Low	Low
	Safety	Low	Low	Low	Low	Low	Low

References

1. Ferguson M, Schwarz TF, Núñez SA, et al; the RSV OA=ADJ-018 Study Group. Noninferior Immunogenicity and consistent safety of respiratory syncytial virus prefusion f protein vaccine in adults 50–59 years compared to ≥60 years of age. *Clinical Infectious Diseases* 79;4:1074-1084.