

RSV Older Adults Briefing Document

Phase III Overview

Respiratory Syncytial Virus (RSV) is one of the major remaining infectious diseases for which there is currently no adult vaccine or specific treatment¹, representing a significant unmet medical need.

It is a common and highly contagious respiratory virus that affects the lungs and breathing passages and is a significant source of respiratory illness, especially for Older Adults (OA) and vulnerable adults with comorbidities.^{1,2}

For more than 50 years, scientists have been trying to develop an RSV vaccine for adults, but so far without success.

Scientific innovation has led to significant recent advances in vaccine development for RSV. In a large pivotal phase III trial, our RSV OA vaccine candidate offered exceptional protection for adults aged 60 and above from the serious consequences of RSV infection with consistent high vaccine efficacy observed across severe RSV disease (94.1%), adults aged 70-79 years (93.8%), adults with underlying comorbidities (94.6%) and across RSV A and B. Overall vaccine efficacy was 82.6% against RSV lower respiratory tract disease (RSV-LRTD).

Across multiple studies, the RSV OA vaccine candidate was well tolerated with a favourable safety profile. **Regulatory submissions based on the phase III data are anticipated in the second half of 2022** marking an important advance in our effort to get ahead of RSV.



High burden of RSV disease and lack of available solutions.

Common and highly contagious respiratory virus.

Significant source of respiratory illness especially for older adults and vulnerable adults with comorbidities.

Aging results in lowered immune responsiveness, and several comorbidities, such as respiratory and cardiovascular disease and diabetes, increase the risk of severe illness due to RSV.^{1,2}

RSV can have a long-term impact on adults 60 years of age and older. The outcomes that result can be severe and irreversible.



In industrialised countries, RSV is estimated to cause over

420,000
hospitalisations

29,000
deaths annually in adults
60 years of age and older.¹



In the US alone, each year RSV infections account for:

177,000
hospitalisations

14,000
deaths in the over
65 population³

Ahead Together

The challenge of protecting older adults

Older adults, as a cohort, is a very large and growing population. In the US alone, there are an estimated 70 million people aged 60 plus and RSV infections account for ~177,000 hospitalisations and ~14,000 deaths in the over 65 population each year.³

In older adults, it is challenging to achieve high levels of protection against severe RSV infections due to age-related decline in immunity and aging of the lung. A weakened immune system makes adults 60 years of age and older vulnerable, as age-related declines in cell-mediated immunity increase susceptibility to infection and enhance disease progression.⁶

Aging reduces pulmonary function and causes a weakening of epithelial integrity, that compromises the ability of aged individuals to fight off respiratory pathogens.

Older adults and comorbidities

In adults, the highest burden of RSV disease is in those aged 60 years and over and those with comorbidities (e.g. lung or heart diseases, diabetes).^{7,8} RSV can exacerbate chronic obstructive pulmonary disease (COPD), asthma and chronic heart failure. In adults hospitalised in the US with RSV, 94% had underlying medical conditions, with hospitalisation rates much higher in those with congestive heart failure.⁹

Older adults hospitalised with RSV may develop acute functional decline, with many requiring a higher level of care at discharge than before.¹⁰

60+

The highest burden of RSV disease is in those aged 60 and over



The virus, how it works, and our vaccine technology

Vaccination offers a solution to RSV, to help improve health outcomes and reduce healthcare costs. Only recently has science progressed enough for us to have precise information about the identity of the best antigen to develop a successful vaccine. Where there had been limited success with a post-fusion RSV F protein (PostF) which hid critical neutralising sites, the new generation pre-fusion RSV F protein (PreF) exposes multiple essential neutralising sites.

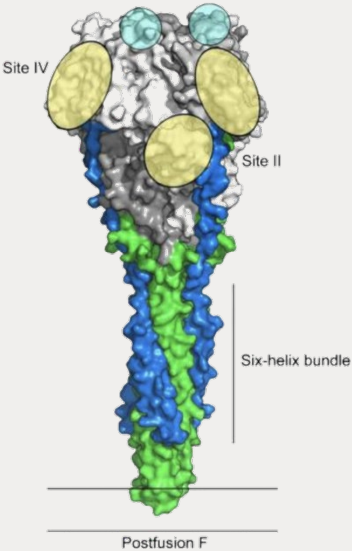
We have over 20 years of acquired experience in assessing T-cell immunity and are using an established technology approach in our RSV older adult (OA) vaccine. The vaccine is designed to overcome the challenges associated with protecting adults at increased risk for severe outcomes due to age or comorbidity.

Older adults are less responsive to vaccination due to age-related decline in immunity, specifically their T-cell response. T-cells may be an important component of the immunity needed to prevent severe respiratory disease, especially in at-risk populations. Therefore, preventing severe RSV in older adults, and older adults with underlying conditions, may require a combination of neutralising antibodies (nAbs) and T-cell responses.

We are combining the pre-F antigen, RSVPreF3, with our adjuvant platform, AS01. The unique antigen/adjuvant combination is designed to deliver high efficacy in adults at risk due to age or comorbidity.

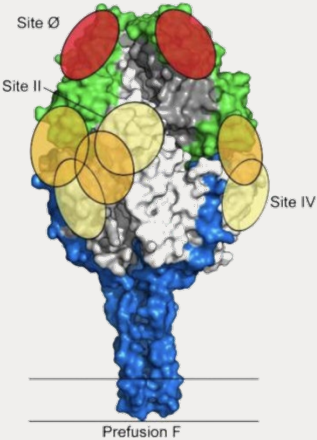
This is an approach already successfully established in other vaccines, including our shingles vaccine, *Shingrix*.

Previous approach



Limited success with post fusion RSV F protein which hides critical neutralising sites

GSK approach



New generation pre fusion RSV F protein exposes multiple essential neutralising sites

Key: Value as target for potent neutralising antibody

● Outstanding	● Excellent	● Good	● Poor
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The AReSVi-006 trial

In June 2022, GSK became the first company to announce positive pivotal phase III results for an RSV vaccine.

Results of the pivotal phase III AReSVi-006 trial show our RSV OA vaccine candidate offered exceptional protection for adults aged 60 and above from the serious consequences of RSV infection with consistent very high vaccine efficacy observed against RSV-lower-respiratory tract disease (RSV-LRTD) across severe disease (94.1%), adults aged 70-79 years (93.8%), adults with underlying comorbidities (94.6%) and across RSV A (84.6%) and B (80.9%). Overall vaccine efficacy was 82.6% against RSV RSV-LRTD, meeting the trial's primary endpoint. In general, the vaccine candidate was well tolerated with a favourable safety profile. The observed solicited adverse events were typically mild- to-moderate and transient with the most frequent being injection site pain, fatigue, myalgia, and headache.

The AReSVi-006 trial will continue to evaluate both an annual revaccination schedules as well as longer term protection over multiple seasons following one dose of the RSV OA candidate.

Around
25,000
patients

have been
enrolled in the
trial from across
17 countries

Regulatory
filings
beginning

H2
2022



Consistent high vaccine efficacy across a range of endpoints

94.1%

Reduction
in severe
RSV-LRTD

94.6%

Efficacy in
adults with
underlying
comorbidities

93.8%

Efficacy in
adults aged
70-79 years

Consistent efficacy across both RSV A and RSV B.

In general, the vaccine was well tolerated with a favourable safety profile. The observed solicited adverse events were typically mild-to-moderate and transient with the most frequent being injection site pain, fatigue, myalgia, and headache.

Additional GSK RSV older adult trials and supporting evidence

AReSVi-006 is part of a comprehensive RSV evidence generation programme being conducted by GSK. Alongside it, we have additional trials and data as part of our comprehensive evidence generation plan:

Trial name (population)	Phase	Design and primary efficacy endpoint(s)	Timeline	Status
RSV OA-004 (Adults ≥60 yo) NCT04732871	III	Randomised, open-label, multi-country study to evaluate the immunogenicity, safety, reactogenicity and persistence of a single dose of the RSVPreF3 OA investigational vaccine and different revaccination schedules in adults aged 60 years and above. 1,720 participants. Primary endpoint: Humoral immune response in terms of RSV-A / RSV-B neutralizing antibody Geometric Mean Titers (GMTs)	Trial start: Q1 2021	Completed: Results showed that, in participants aged 60 years and above, one dose of the RSV OA investigational vaccine induced strong humoral and cellular immune responses, which remain above pre-vaccination levels up to at least the six months post vaccination readout timepoint.
RSV OA-006 (Adults ≥60 yo) NCT04886596	III	Randomised, placebo-controlled, observer-blind, multi-country study to demonstrate the efficacy of a single dose of GSK's RSVPreF3 OA investigational vaccine in adults aged 60 years and above. 25,000 participants. Primary endpoint: Number of participants with first episode of RT-PCR confirmed RSV A and/or B associated LRTD during the first season following a single dose of the RSVPreF3 OA vaccine	Trial start: Q2 2021	Completed: Primary endpoint was exceeded with no unexpected safety concerns observed.
RSV OA-007 (Adults ≥60 yo) NCT04841577	III	Open-label, randomised, controlled, multi-country study to evaluate the immune response, safety and reactogenicity of RSVPreF3 OA investigational vaccine when co-administered with FLU-QIV vaccine in adults aged 60 years and above. 976 participants. Primary endpoints: • RSV-A neutralization antibody titers expressed as group Geometric Mean Titer (GMT) ratio • Hemagglutinin inhibition (HI) antibody titers expressed as group GMT ratio	Trial start: Q2 2021	Completed: Positive data demonstrated that co-administration has little impact on either RSV or flu immune responses.
RSV OA-009 (Adults ≥60 yo) NCT05059301	III	Randomised, double-blind, multi-country study to evaluate consistency, safety, and reactogenicity of 3 lots of RSVPreF3 OA investigational vaccine administered as a single dose in adults aged 60 years and above. 757 participants. Primary endpoint: RSVPreF3 specific immunoglobulin (Ig)G antibody concentrations expressed as group geometric mean concentration (GMC) ratio at 30 days post-vaccination	Trial start: Q4 2021	Active: Not recruiting.

Overview of trials testing efficacy of RSV vaccines in older adults

The development of RSV vaccine candidates in the adult setting is evolving rapidly. Different technology platforms eliciting different mechanisms of action are being developed by several companies for prevention of RSV associated illness in older adults. While GSK’s vaccine is an adjuvanted subunit vaccine different companies are developing either unadjuvanted subunit vaccines, viral vector vaccines or mRNA vaccines in late-stage studies.

Company, Asset and technology	Trial name (population)	Phase	Design and primary efficacy endpoint(s)	Status
Pfizer – PF-06928316 Subunit preF protein without adjuvant	RENOIR (Adults ≥60 yo) NCT05035212	III	Randomized, double-blinded, placebo-controlled study designed to assess the safety, immunogenicity, and efficacy of RSVpreF in the prevention of LRTI-RSV. 37,609 participants. Primary endpoints: • Number of first episode of RSV-associated lower respiratory tract illness (LRTI-RSV) in the first RSV season (average of 6 months) • Proportion of participants reporting AEs	Study completion: 2023
Bavarian Nordic – MVA-BN-RSV MVA vector expressing different RSV antigens	VANIR (Adults ≥60 yo) NCT05238025	III	Randomized, double blind study comparing recombinant MVA-BN-RSV vaccine vs placebo for efficacy and safety. 20,000 participants. Primary endpoint: Occurrence of LRTD (at least 6 months, and up to 12 months post vaccination)	Ongoing. Primary completion: November 2023 Study completion: December 2024
Moderna – mRNA-1345 mRNA expressing preF protein	ConquerRSV (Adults ≥60 yo) NCT05127434	II/III	Study to evaluate the safety and tolerability of mRNA-1345 vaccine and to demonstrate the efficacy of a single dose of mRNA-1345 vaccine in the prevention of a first episode of RSV-associated lower respiratory tract disease (RSV-LRTD). 34,000 participants. Primary endpoints: • Vaccine Efficacy (VE) of mRNA-1345 to prevent a first episode of RSV-LRTD within the period of 14 Days post injection up to 12 months post injection • Number of Participants with AEs	Ongoing. Primary completion: December 2023 Study completion: November 2024

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Overview of trials testing efficacy of RSV vaccines in older adults (continued)

Company, Asset and technology	Trial name (population)	Phase	Design and primary efficacy endpoint(s)	Status
Janssen/JNJ – JNJ-64400141 Adenovector expressing preF combined with preF subunit	CYPRESS (Adults ≥65 yo) NCT03982199	IIb	Study to demonstrate the efficacy of active study vaccine in the prevention of reverse transcriptase polymerase chain reaction (RT-PCR) confirmed respiratory syncytial virus (RSV)-mediated lower respiratory tract disease (LRTD), when compared to placebo. 5,815 participants. Primary endpoint: Percentage of participants with protocol defined RSV-mediated LRTD confirmed by RT-PCR (Up to 1.6 years)	Ongoing. Primary completion: June 2022 Data presented Sept 2022 Study completion: May 2024
	EVERGREEN (Adults ≥60 yo) NCT04908683	III	Study of an Adenovirus Serotype 26 Pre-fusion Conformation-stabilized F Protein (Ad26. RSV. preF) Based RSV Vaccine in the Prevention of Lower Respiratory Tract Disease. 27,500 participants. Primary endpoint: Percentage of participants with protol defined RSV-mediated LRTD confirmed by RT-PCT (Up to 24 months)	Ongoing. Primary completion: June 2023 Study completion: November 2024
	(Adults 18 to 59 yo including Adults at High Risk for Severe RSV Infection) NCT05070546	III	Study to investigate safety and immunogenicity of the Ad26.RSV.preF based vaccine in adults 18 to 59 years of age who are healthy or at risk for severe Respiratory Syncytial Virus (RSV) disease, compared to adults 65 years and above. 1,124 participants. Primary endpoints: • Number of Participants with AEs • Neutralizing Antibody Titers Against RSV A2 Strain as measured by Virus Neutralization Assay (VNA) (at 15 days) • Seroresponse Rate After Vaccination as Determined by VNA A2 (at 15 days)	Completed. Study completion: August 2022

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