



Newsletter

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WELCOME TO THE SECOND ISDB NEWSLETTER OF 2025

This second issue of 2025 includes updates on following ISDB members’ published articles:

- An article from DTB Navarre providing an in-depth analysis on the validity of surrogate outcomes and the consequences of fast-track approvals.
- An article from Der Arzneimittelbrief on treatment of Multiple myeloma with CAR-T cell therapy.
- An article from Prescrire International on RSV vaccines from 60 years of age.

You will also find information on a recently published article from Common Sense Oncology published in the Lancet Oncology focusing on principles for the design, analysis, and reporting of phase 3 randomised clinical trials.

Below you get a glimpse on the provisional program of the General Assembly meeting in Verona (Italy) early October 2025. Practical information will follow soon by email.

Provisional draft program of the General Assembly (GA), Verona (Italy)

Wednesday, 1st October 2025	
1 pm	Registration
1.30-3.30 pm	Inaugural session : Contextualisation of the ISDB principles in the current environment
3.30 - 4 pm	Coffee break
4-6 pm	Presentation and discussion of the ISDB strategic plan
Evening	Get-Together dinner
Tuesday, 2 nd October 2025	
9-10.30 am	Health Technology Assessment: a big reform in the European Union with the launch of joint clinical assessments - Challenges for evidence requirements and transparency
10.30-11.00 am	Coffee break
11.00-12.30 am	Training session on “emulated trials”. Usefulness, pitfalls and dangers in the use of emulated trials
12.30-2.00 pm	Lunch
2.00 - 4.00 pm	Lessons from the unknown, the expected, the false, the hidden and, maybe, the worthwhile: The Covid-19 vaccines case
4.00-4.30 pm	Coffee break
4.30-6.00 pm	The framing of obesity as a disease and obesity drugs
Friday, 3 rd October 2025	
9- 12.30 am	ISDB internal affairs: GA including the election of the executive committee

Surrogate outcomes and fast-track drug approval. Towards reversing the burden of proof?

Public Citizen, October 28, 2024



DRUG AND THERAPEUTICS
BULLETIN OF NAVARRE,
SPAIN

The Spanish drug bulletin DTB Navarre has recently published an in-depth analysis on the validity of surrogate outcomes and the consequences of fast-track approvals. The fundamental objective of any therapeutic intervention is to exert the clinically relevant effect for which it was designed in its target population, while presenting an acceptable risk of undesirable events and a cost consistent with the real value provided. Taking this into account, the methodology adopted to determine that an intervention is effective interests and concerns us all.

Until the beginning of the 2010s, the requirement of high clinical significance when considering the efficacy outcomes for a clinical trial with regulatory implications has been the standard rule. These are what are known as “hard” outcomes. However, sometimes long time periods and high costs are inherent to obtaining these parameters. As a consequence, regulatory requirements have been changing and other types of outcomes, known as “surrogates”, have been gaining traction recently. These are theoretically correlated with the hard outcomes but are simpler and faster to collect, although they lack the genuine clinical interest of outcomes with a real impact on the population.

A wide range of terms are used in the scientific literature to describe and quantify the extent of the effects derived from therapeutic interventions (biological marker, biomarker, surrogate marker, surrogate outcome, intermediate outcome...). This has resulted in some overlap and ambiguity. To our purpose, a surrogate outcome can be defined as a variable that is expected to predict the benefit or harm of the therapy by replacing the clinical outcome, since it is considered that direct measurement of the effect is not feasible or practical. In an ideal scheme, the surrogate outcome would reflect the entire effect that the treatment exerts on the clinical outcome of interest. Unfortunately, on many occasions this theoretical relationship does not translate into practice.

The use of surrogate outcomes in clinical trials is a growing phenomenon. Indeed, it has been estimated that less than half of the studies designed to test the efficacy of new drugs in the 1990s used this tool, whereas by 2017 this proportion had already reached 60%. There are three classical criteria to confirm the validity of a surrogate outcome: 1) The surrogate outcome must predict the clinical outcome. 2) The surrogate outcome should fully capture the effect of the treatment on the clinical outcome. 3) The treatment must demonstrate a significant effect on both the surrogate outcome and the clinical outcome. Thus, correlation is not enough to validate a surrogate outcome and data suggest that there is limited interest in taking such validation seriously. Statistics by itself cannot solve the gaps of incomplete knowledge.

The push for surrogate outcomes in the regulatory field has its origins on the other side of the Atlantic. The fast-track approval program for medicines in the US (Accelerated Approval program) was launched in 1992 for drugs that targeted serious diseases and has served as a model for subsequent similar strategies in Europe. In this program, the FDA accepts what it calls a “reasonably likely to predict clinical benefit” outcome. These outcomes do not provide sufficient clinical data and rely





Cover of the BMJ, January 14, 2012.
<https://www.bmj.com/archive/covers/2012>

on subsequent post-authorization studies that, very often, do not come to light. In addition, the benefit of those completed is not encouraging.

The European Medicines Agency (EMA) offers two routes for the fast-track authorization of medicines when it is estimated that there is an unmet medical need or a public health interest, both defined in the first decade of the 21st century. These are conditional marketing authorization and accelerated assessment. Like the FDA, the EMA also allows the use of insufficiently validated surrogate outcomes in clinical trials with an undertaking to carry out subsequent confirmatory studies. Again, unfortunately despite clear institutional regulations, surrogate outcomes rarely demonstrate adequate validation.

The new paradigm in Europe aims to apply what has been started in the restricted accelerated approval programs to all new authorizations. The risk-benefit balance of this deregulation is still unknown, but something can be predicted: the population will access more uncertain therapies sooner, the pharmaceutical industry will access the benefit sooner, funders will pay sooner (and more?) due to treatments with difficult therapeutic positioning, and pharmacovigilance will have difficulties in mitigating the impact of harm derived from

therapies that quickly become widespread among the population. In clear contrast with this trend, the German authorities (G-BA and IQWiG) lead the position of establishing greater demands on the requirements for funding.

When some common surrogate outcomes are explored, it can be concluded that HIV viral load or blood pressure are examples of adequately validated variables. On the contrary, important inconsistencies are identified in variables used in the approach to cancer, dementia, osteoporosis and infectious or cardiovascular diseases. Regarding cancer, only 20% of antineoplastic drugs approved on an accelerated schedule show benefit in overall survival. Single-arm studies are also a matter of concern.

Also, not infrequently a marketed drug on the basis of surrogate outcomes had to be withdrawn, or their indications restricted, due to harmful effects in certain clinical situations. It has been the case for drugs approved for cardiovascular, infectious, blood or bone diseases. Thus, we should consider seriously that an early access to a drug is not always equivalent to clinical or social benefit.

We are gradually cutting deadlines and abandoning reliable designs such as the clinical trial. This methodology is able to generate results with solid internal validity. The secret is two-fold: randomization and blinding. Five decades later, the clinical trial is today accused of being excessively slow, rigid, expensive and having external applicability problems. Big data, artificial intelligence algorithms or mathematical modelling, amongst others, promise large sample sizes, data under real or simulated conditions, rapid response and affordable price. But we may end up buying precision when we need reliability. Without clinical trials, without hard clinical outcomes, we have a much greater chance of making erroneous clinical decisions in the future. And what is worse, a greater chance of discarding as outdated the tools that would allow us to become aware of it.

Reference:

Saiz LC. Surrogate outcomes and fast-track drug approval. Towards reversing the burden of proof? DTB Navarre 2025;32(1):1-17. Free access at: <https://doi.org/10.54095/BITN20253201EN>

Treatment of Multiple Myeloma with CAR-T cell therapy

Notice: This text was published in *Der Arzneimittelbrief* in March 2025. It was translated from German to English with support from DeepL©

DER ARZNEIMITTELBRIEF

Immunotherapy of cancer with CAR-T cells is now considered a promising new strategy, particularly for haematological neoplasms such as non-Hodgkin's lymphoma and Multiple Myeloma (MM; 1, 2). As early as 2018, the European Medicines Agency (EMA) approved Kymriah® (tisagenlecleucel) and Yescarta® (Axicabtagene ciloleucel) as the first CAR-T cell therapies for the treatment of blood cancers (1). The Chair of the Committee for Advanced Therapies (CAT), Dr. Martina Schüssler-Lenz, has already expressed a very positive outlook on this novel therapeutic strategy. She regarded it as a new generation of 'personalised cancer immunotherapies', and predicted that it would lead to a fundamental change in the treatment of serious, often fatal diseases (2). However, in our view this prediction was somewhat premature.

CAR-T cell therapies have already been incorporated into standard clinical care and have demonstrated consistent efficacy in the treatment of selected diseases, including MM and malignant lymphomas, as a component of first-line therapy and in cases of subsequent relapses, even in the context of prior chemotherapy. Furthermore, encouraging initial results have been observed in the treatment of various autoimmune diseases through the use of CAR-T cell therapies (3). A detailed report on this subject will be presented in an upcoming edition of DER ARZNEIMITTELBRIEF.

However, as serious side effects can occur during or after this therapy (4, 5), the clinical use of CAR-T cells requires appropriate experience in order to recognise and treat the sometimes life-threatening side effects in time. In addition, CAR-T cell therapies can rarely trigger secondary malignancies, especially T-cell lymphomas (5). In the light of the prevailing concerns, the Paul-Ehrlich-Institut initiated a signal evaluation procedure for CAR-T cell therapies in early 2024 (6). This initiative followed the approval of six CAR-T cell products (Abecma®, Breyanzi®, Carvykti®, Kymriah®, Tecartus® and Yescarta®) in Germany. In view of the suspected case reports available at that time, particularly with regard to the occurrence of T-cell lymphomas, it was considered necessary to investigate a possible connection with this novel cancer immunotherapy, and the risk-benefit ratio should be assessed. The current status and content of this signalling assessment procedure were published on the EMA website (7).

Using the example of the clinical studies published so far on Ciltacaptogene autoleucel (Carvykti®), we would like to briefly present the results currently available with this therapy in the treatment of MM and reiterate the side effects of CAR-T cell therapies (8, 9).

Carvykti® is a pharmaceutical compound that is derived from genetically modified autologous cells containing T cells (T lymphocytes) from the patient. These cells have been transduced *ex vivo* with a replication-incompetent lentiviral vector (8). This vector encodes a chimeric antigen receptor (CAR) directed against the B-cell maturation antigen (BCMA). Carvykti® is administered in a patient-specific infusion bag with a batch-dependent concentration of autologous, genetically modified T-cells in order to recognise the aforementioned chimeric anti-BCMA antigen receptor (CAR-positive viable T cells). The cellular composition and the final number of CAR-T cells depend on the patient's body weight and can therefore vary between the individual patient batches.

Carvykti® is currently indicated for the treatment of adult patients with relapsed and refractory MM who have already received at least 3 prior therapies, including an immunomodulator (e.g. lenalidomide), a Proteasome inhibitor (e.g. bortezomib, carfilzomib) and an anti-CD38 Monoclonal antibody (e.g. daratumumab, isatuximab) and who showed progression of MM during the last therapy (8).

Carvykti® has to be administered in a qualified treatment centre and therapy should be initiated and monitored under the direction and supervision of healthcare professionals (8). This is particularly important as specific, sometimes life-threatening side effects can occur after the infusion. These include in particular, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and the very frequent occurring immune effector cell-associated hematotoxicity' (ICAHT; 9, 10).

In 2024 the German Association for Haematopoietic Stem Cell Transplantation and Cellular Therapy e.V. (DAG-HSZT) published an analysis regarding the management of side effects that occurred after CAR-T cell therapy at 17 centres and revealed significant differences in the treatment of CRS, ICANS, immunoglobulin substitution, administration of autologous stem cells as 'backups' and the implementation of infection prophylaxis as well as vaccinations (10). This publi-

cation therefore rightly called for more prospective studies to be carried out, not only to evaluate the results of CAR-T cell therapies, but above all to provide evidence-based recommendations for supportive treatment.

Study overview: The clinical studies CARTITUDE-1 (Phase Ib/II) and CARTITUDE 4 were taken into account in the authorisation decision of Carvykti® (11, 12). In the single-arm, uncontrolled CARTITUDE-1 trial, patients with MM and at least 3 prior therapies or patients who were refractory to both, an immunomodulator and a Proteasome inhibitor, were treated with a single infusion of Carvykti®. This prolonged the median progression-free survival (PFS) to 34.5 months. The achievement of complete remission (CR) and/or sustained negativity of minimal residual disease (MRD) was associated with a prolonged PFS. The further course (safety and survival) of the patients will be analysed in the ‘CARTITUDE long-term study’, which is planned for 15 years.

In the ongoing, open-label phase III trial (CARTITUDE-4; 12), Carvykti® is used in 208 patients from 81 clinics in the USA, Europe, Asia and Australia (recruitment from July 2020 until November 2021). Compared to ‘standard care’, Carvykti® improved the ‘Health-related Quality of Live’ (= QOL: holistic view of the patient’s health status) and delayed the onset of the disease.

In a systematic review and meta-analysis of non-relapse mortality (NRM) after CAR-T cell therapy recently published in Nature Medicine, a total of 7,604 patients from 18 clinical trials and 28 real-world studies were included (13). The NRM differed between MM and the various subtypes of malignant lymphomas. It was highest in mantle cell lymphoma (10.6%) followed by MM (8.0%) and the large B-cell lymphomas (6.1%). Both axicabtagene ciloleucel (Yescarta®) and Carvykti® were more frequently affected by NRM than the other subtypes of malignant lymphomas. The main causes of NRM were infections (50.9%), followed by other malignancies (7.8%) and cardiovascular or respiratory side effects (7.3%). In contrast, the side effects specific to CAR-T cell therapy (e.g. CRS, ICANS) were only rarely responsible for deaths.

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NEW SUBSTANCE

RSVPreF3/AS01_E vaccine (AREXVY[®]) in the prevention of RSV infections from 60 years of age

Insufficient evidence of efficacy in the prevention of severe infections, in particular in those at highest risk



NOTHING NEW

In a randomised trial in 24 966 adults aged 60 years or older, RSV-associated lower respiratory tract infections were reported in 0.05% of participants in the RSVPreF3/AS01_E vaccine group, versus 0.3% in the placebo group (an estimated vaccine efficacy of 83%). The trial was not designed to demonstrate efficacy in adults aged 80 years or older, nor in preventing severe infections, defined as those resulting in hospitalisation, oxygen supplementation or mechanical ventilation. The main adverse effects of the vaccine were local and systemic reactions. 2 cases of Bell's palsy and 1 case of Guillain-Barré syndrome were reported during the trials. Atrial fibrillation appeared to occur more frequently in the vaccine group. As of mid-2024, given the lack of demonstrated efficacy in preventing severe RSV infections, there is no justification for exposing all adults aged 60 years or older to the potentially serious adverse effects of the RSVPreF3/AS01_E vaccine. And the evidence that RSVPreF3/AS01_E represents a therapeutic advance in those at highest risk is no more convincing, due to the uncertainties about its efficacy in preventing severe infections, and to a possible increased incidence of immune disorders and atrial fibrillation.

AREXVY[®] - RSVPreF3/AS01_E vaccine powder and suspension for suspension for intramuscular injection

- **120 microg** of RSV F antigen + **50 microg** of AS01_E adjuvant (consisting of QS-21 and MPL). Once reconstituted, the vial contains one 0.5-ml dose.

GlaxoSmithKline Biologicals

■ Adjuvanted RSV vaccine

- **Indication:** "active immunisation for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 60 years of age and older". [EU centralised procedure]

- **Dosage:** a single dose of 0.5 ml.

- **Storage conditions:** between 2°C and 8°C, protected from light. Once reconstituted, the vaccine must be administered immediately, or within 4 hours if it is stored between 2°C and 25°C.

Compare before deciding

Respiratory syncytial virus (RSV) infections do not only cause bronchiolitis in infants, but can occur at all ages, not least because infection-acquired immunity is temporary (1).

In primary care in France during the 2021-2022 RSV season, the main viruses involved in acute respiratory infections, across all age groups, were influenza viruses (29% of cases), Sars-CoV-2 (14%) and RSV (4%). The incidence of acute respiratory infections for that RSV season has been estimated at 377 per 10 000 adults aged 65 years or older. These data are highly approximate since these infections are not routinely confirmed by laboratory testing. According to a retrospective study of adults hospitalised with a diagnosis of RSV infection between 2012 and 2021, about 8% were aged 50 to 59 years, and 83% were aged 60 years or older. According to this study and another retrospective study conducted between 2015 and 2019 in patients aged 63 years or older hospitalised for an RSV-related condition, RSV-associated mortality was estimated at about 7% (2,3).

According to a systematic review of 24 trials conducted in adults aged 60 years or older living in industrialised countries, the incidence of RSV infection during the RSV season was estimated at 110 per 10 000, and the incidence of RSV-related hospitalisation at 13 per 10 000 (1).

In adults: acute respiratory infections, with no specific signs.

RSV infections are almost always symptomatic. In adults, they present as acute respiratory infections, including the following: systemic symptoms (fever, asthenia and anorexia); signs of upper respiratory tract disease (nasal congestion, rhinorrhoea and sore throat); and sometimes signs of lower respiratory tract disease, which is common in older adults (cough, sputum, wheezing and dyspnoea). These respiratory infections can lead to decompensation of a pre-existing condition, or acute respiratory distress requiring respiratory support. In some cases, they can be fatal (2-5).

The risk factors for severe RSV infection are: advanced age; tobacco exposure; a pre-existing condition such as congestive heart failure, chronic obstructive pulmonary disease (COPD) or asthma; and immunosuppression, caused in particular by immunosuppressive treatment for cancer or following an organ transplant (3-5).

Prevention of RSV infections: centred on general measures designed to reduce the spread of viruses.

Prevention of RSV infections is mainly based on general measures designed to reduce the spread of the viruses that cause respiratory infections, in particular frequent handwashing, and potentially wearing a mask if it is not possible to avoid coming

MARKETING AUTHORISATIONS

into close contact with people who are infected or possibly infected. These measures are beneficial during the period of high viral circulation, in particular for those at high risk of severe RSV infection (4).

What's new?

In the European Union, the *RSVPreF3/AS01_E* vaccine is the first vaccine authorised for use in adults aged 60 years or older for the prevention of RSV-associated lower respiratory tract infections. It contains RSV F protein, which is made up of 3 subunits (hence the "F3" in its name), stabilised in its form prior to fusion of the virus with host cells (hence "PreF", which stands for "pre-fusion").

Another RSV vaccine, the *RSVPreF* vaccine, also contains F protein antigen in its "pre-fusion" form. It was originally authorised for use during pregnancy to prevent RSV infection in the woman's child after birth, and it has since been authorised for use in adults aged 60 years or older (see "RSVPreF vaccine (Abrysvo[®]) in the prevention of RSV infections from 60 years of age" pp. 8-9) (1,3,6).

The *RSVPreF3/AS01_E* vaccine contains two adjuvants: MPL and QS-21, a combination known as AS01_E. MPL is used in other vaccines, in particular the human papillomavirus vaccine Cervarix[®], and AS01_E is used in the malaria vaccine Mosquirix[®] (1,7).

In adults aged 60 years or older, does the *RSVPreF3/AS01_E* vaccine prevent respiratory infections? Does it reduce hospitalisations and mortality? And what are its adverse effects?

A placebo-controlled trial in about 25 000 people.

The clinical evaluation of the *RSVPreF3/AS01_E* vaccine is mainly based on a single-blind (observer-blind) randomised placebo-controlled trial (1,5,8).

This trial was conducted in 17 countries in both the northern and southern hemispheres. It enrolled 24 966 people from May 2021 onwards, with follow-up during 2 or 3 RSV seasons depending on the hemisphere. Immunocompromised persons were excluded from the trial (1,5).

At baseline, three-quarters of the participants were aged 65 years or older (median age 69 years), and 8% were aged 80 years or older. 1% of participants were living in a long-term care facility, and about 20% had a cardiorespiratory condition (such as COPD, asthma or chronic heart failure) (1,5,8).

A reduction in the number of RSV-associated lower respiratory tract infections: reported in 0.05% of vaccinees versus 0.3% in the placebo group.

Half of the participants were followed up for at least 7 months, from day 15 after the initial injection. The preventive efficacy of the vaccine was evaluated based on the number of people who developed an RSV-associated lower respiratory tract infection. These infections were defined based on patient-reported symptoms (such as cough and dyspnoea), and signs observed by a health professional (such as wheezing, crackles on chest auscultation, increased respiratory rate and decreased oxygen saturation). An RSV-associated lower respiratory tract infection was thus defined by the presence of at least 3 symptoms, or at least 2 signs, or 1 sign and 1 symptom, for a period of 24 hours or more, alongside laboratory confirmation of the infection by RT-PCR (reverse transcriptase polymerase chain reaction) testing. From day 15 after the injection onwards, 7 people (0.05%) had an infection of this type in the vaccine

group versus 40 (0.3%) in the placebo group, representing a statistically significant reduction in the risk of RSV-associated lower respiratory tract infection of about 83% (1,5,9,10).

The number of trial participants aged 80 years or older was too small to demonstrate the vaccine's efficacy in this age group (1,5).

No evidence of benefit from a booster dose 1 year after the initial dose.

About 80% of participants remained in the trial during a second consecutive RSV season. Before this second season, about half of those in the vaccine group received a booster dose of the vaccine. The other participants in this group and those in the placebo group received an injection of placebo. Half of the participants were followed up for at least 18 months, from day 15 after the initial injection.

During this second RSV season, in the group that had received a single dose of vaccine (without a booster), 30 people (0.2%) had an RSV-associated lower respiratory tract infection, versus 139 (1.1%) in the placebo group. This reduction in the relative risk of infection of about 67% was statistically significant (10,11). The preventive efficacy of the *RSVPreF3/AS01_E* vaccine appeared to be similar in participants who had received only a single dose during the previous RSV season, and in those who had received a booster dose (10).

Unclear efficacy against the rare severe infections requiring hospitalisation, oxygen supplementation or mechanical ventilation.

The trial was not designed to evaluate the efficacy of the vaccine in preventing severe RSV infections, defined as those requiring hospitalisation, oxygen supplementation or assisted ventilation (1,5,11).

According to the trial protocol, infections were considered to be "severe" if at least 2 clinical signs of lower respiratory tract infection were present, with investigators' opinions also taken into account. But according to the analysis by the European Medicines Agency (EMA), the presence of 2 signs of lower respiratory tract infection is not sufficient to categorise an infection as severe. Therefore, in the view of the EMA, some of the cases that were considered severe by the investigators were not in fact severe (1,5).

During the first RSV season, 1 person had a "severe" RSV infection (as defined in the trial protocol) in the vaccine group versus 17 people in the placebo group, representing a statistically significant reduction in the risk of such an infection of about 94%. 2 people required supplemental oxygen or ventilatory support, and 1 person in the placebo group was hospitalised for an RSV-related disorder, versus none in the vaccine group (1,5).

Over the course of the 2 RSV seasons, 14 participants had a "severe" RSV infection (as defined in the trial protocol) in the vaccine group (7 people who had received one dose, and 7 who had received two doses) versus 48 in the placebo group, representing a statistically significant reduction in the relative risk of such an infection of about 79%. 1 person required supplemental oxygen or assisted ventilation and 1 person was hospitalised in the vaccine group, versus 5 and 5 respectively in the placebo group (1,5). The documents that we identified do not specify whether the participants who required supplemental oxygen were the same as those who were hospitalised. No RSV-related deaths were reported (10,11).

MARKETING AUTHORISATIONS

Frequent local and systemic reactions, and possibly an increased incidence of immune disorders and atrial fibrillation. The foreseeable adverse effects of the *RSVPreF3/ASO1_E* vaccine are the same as those of the *RSVPreF* vaccine, i.e. those common to all vaccines (local injection-site reactions and systemic reactions). Autoimmune diseases such as Guillain-Barré syndrome, a few cases of which have been observed with some vaccines, are also a possibility (6).

In the trial in 24 966 participants, short-term reactions to the vaccine were evaluated in the 4 days following the initial injection in 1757 participants. Injection-site reactions, in particular pain, were reported in 62% of vaccinees versus 10% in the placebo group. Systemic reactions were reported in 49% of vaccinees versus 23% in the placebo group, in particular fatigue (34% versus 16%), muscle pain (29% versus 8%) and headache (27% versus 13%). Severe local and systemic reactions were reported in 5.6% of vaccinees versus 0.9% in the placebo group (1,5).

Across all trial participants, in the 30 days after the first vaccination, 10 cases of atrial fibrillation (7 serious) were reported in the vaccine group versus 4 (1 serious) in the placebo group. A causal association with the vaccination cannot be ruled out (1,5).

In a pooled analysis of 3 trials in about 24 000 participants followed up for 6 months after vaccination, an immune disorder was reported in 53 vaccinees (0.4%) versus 34 (0.3%) in the placebo groups. In the vaccine groups, 1 case of Guillain-Barré syndrome and 2 cases of Bell's palsy were reported. A causal association between these cases and the *RSVPreF3/ASO1_E* vaccine was assessed by the US Food and Drug Administration (FDA) as being possible (5,11).



Concomitant administration with a seasonal influenza vaccine: weaker immune response with uncertain clinical consequences.

In a randomised immunogenicity trial in 885 adults aged 60 years or older, the *RSVPreF3/ASO1_E* vaccine and a seasonal influenza vaccine were administered either concomitantly or a month apart. In this trial, immune response to RSV or the seasonal flu virus was lower when both vaccines were administered at the same time. The clinical consequences of this lower immune response are unknown (1,5). Despite the reassurance given in the European summary of product characteristics (SmPC), it is therefore advisable to avoid concomitant administration of these two vaccines.

Assessment elsewhere

The clinical evaluation data on the *RSVPreF3/ASO1_E* vaccine have also been examined by the French National Authority for Health (HAS) and by other teams working independently of the pharmaceutical industry. Some of their conclusions are reproduced below (our translations where necessary).

HAS (France). In its opinion of 27 June 2024, "the HAS recommends seasonal vaccination against RSV in subjects aged 75 years or older, in order to reduce the number of RSV-associated acute lower respiratory tract infections. The HAS considers that the *Arexvy* vaccine and *Abrysvo* vaccine can be used in the context of this recommendation. In addition, the HAS recommends vaccination in subjects aged 65 years or older with chronic respiratory disease (particularly COPD) or

cardiovascular disease (particularly heart failure) at risk of decompensation due to RSV infection" (12).

Arznei-Telegramm (Germany). "The incidence of RSV-associated lower respiratory tract infections is only 0.09% to 0.3%. The efficacy of vaccination against the severe complications of these infections requiring hospitalisation, oxygen and/or mechanical ventilation, observed sporadically in the trials, has not been demonstrated. Atrial fibrillation [and] Guillain-Barré syndrome are adverse effects requiring more in-depth analysis" (13).

Der Arzneimittelbrief (Germany). "There appears to be no justification for vaccinating all adults aged 60 years or older against RSV. Other trials should be conducted in the groups of people concerned" (14).

The Medical Letter (United States). "A single dose of either vaccine appears to be effective in preventing RSV-associated lower respiratory tract disease for one, and possibly two, RSV seasons in adults ≥60 years old. Atrial fibrillation and inflammatory neurologic events such as Guillain-Barré syndrome have been reported following vaccination. Until more safety data become available, the CDC Advisory Committee on Immunization Practices (ACIP) recommends targeting vaccination to older adults at highest risk for severe RSV disease [adults aged 75 years or older, or aged 60 to 74 years with a chronic medical condition, in particular lung or heart disease, or living in a nursing home]" (15,16).

In practice

In adults aged 60 years or older, RSV respiratory infections can, in rare cases, cause acute respiratory distress requiring respiratory support, and even more rarely can be fatal. In a placebo-controlled clinical trial evaluating the *RSVPreF3/ASO1_E* vaccine in about 25 000 people, a reduction in the risk of RSV infection was reported. But this trial was not designed to demonstrate whether the vaccine provides any benefit in adults aged 80 years or older, nor in preventing severe infections, i.e. those resulting in hospitalisation, oxygen supplementation or assisted ventilation. No RSV-related deaths were reported during the trial, including in the placebo group. The adverse effects of the *RSVPreF3/ASO1_E* vaccine are those common to all vaccines, but atrial fibrillation and immune disorders, in particular autoimmune disorders such as Bell's palsy and Guillain-Barré syndrome, were more frequent in vaccinees during the trials.

In summary, as of mid-2024, the *RSVPreF3/ASO1_E* vaccine has not been shown to represent a therapeutic advance in the prevention of severe RSV infections, in particular among adults at highest risk. General measures designed to reduce the spread of the viruses that cause respiratory infections remain the first-choice strategy during the period of high viral circulation, in particular for people at high risk of severe RSV infection.

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January 2025, Volume 34 - Issue 266 p. 5-8

MARKETING AUTHORISATIONS

Literature search up to 24 June 2024



In response to our request for information, GlaxoSmithKline Biologicals provided us with published documents, administrative information and packaging items.

- 1- EMA - CHMP "Public assessment report for Arexvy. EMEA/H/C006054/0000" 26 April 2023: 103 pages.
- 2- Loubet P et al. "Respiratory syncytial virus-related hospital stays in adults in France from 2012 to 2021: A national hospital database study" *J Clin Virol* 2024; **171**: 8 pages.
- 3- HAS "Stratégie vaccinale de prévention des infections par le VRS chez l'adulte âgé de 60 ans et plus" 21 December 2023: 16 pages.
- 4- Piedimonte G and Anderson M "Respiratory syncytial virus infection" *BMJ Best Practice* 4 October 2023: 65 pages.
- 5- US FDA - CDER "Application number STN125775.0. BLA clinical review memorandum" 3 May 2023: 75 pages.
- 6- Prescrire Editorial Staff "RSVpreF vaccine (Abrysvo®) during pregnancy to prevent RSV infection in the woman's child after birth. Fewer severe infections and hospitalisations, but more preterm births and many unknowns" *Prescrire Int* 2024; **33** (258): 89-92.
- 7- Prescrire Editorial Staff "RT,S,AS01E malaria vaccine. Children living in malaria-endemic regions: little efficacy, poorly documented harms" *Prescrire Int* 2017; **26** (178): 5-8.
- 8- Papi A et al. "Respiratory syncytial virus prefusion F protein vaccine in older adults" *N Engl J Med* 2023; **388** (7): 595-608 + protocol: 793 pages.
- 9- Dictionnaire médical de l'Académie de médecine "Signe". www.academie-medecine.fr accessed 12 June 2024.
- 10- Ison MG et al. "Efficacy and safety of Respiratory Syncytial Virus (RSV) Prefusion F protein vaccine (RSVPreF3 OA) in older adults over 2 RSV seasons" *Clin Infect Dis* 22 January 2024: 13 pages.
- 11- US CDC - Advisory Committee on Immunization Practices "Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): GSK RSVPreF3 vaccine (AREXVY)" 20 July 2023: 12 pages.
- 12- HAS "Stratégie vaccinale de prévention des infections par le VRS chez l'adulte âgé de 60 ans et plus" 27 June 2024: 183 pages.
- 13- "RSV-Impfstoffe Abrysvo und Arexvy für Erwachsene ab 60 Jahre" *Arznei-Telegramm* 2023; **54** (10): 73-5.
- 14- "Infektionen mit dem respiratorischen synzytial-Virus (RSV)-neuere Entwicklungen zur Prävention" *Der Arzneimittelbrief* 2024; **58** (35): 2 pages.
- 15- "Two vaccines (Arexvy and Abrysvo) for prevention of RSV disease" *Med Lett Drugs Ther* 2023; **65** (1686): 153-155.
- 16- CDC "CDC updates RSV vaccination recommendation for adults" 26 June 2024. www.cdc.gov accessed 1 July 2024: 2 pages.

NEW INDICATION

RSVPreF vaccine (ABRYSVO®) in the prevention of RSV infections from 60 years of age



NOTHING NEW

In a randomised placebo-controlled trial in about 34 000 people, the RSVPreF vaccine was not shown to be effective in preventing severe RSV infections, in particular in those at highest risk. As of mid-2024, given its potentially serious adverse effects, this vaccine does not represent a therapeutic advance.

ABRYSVO® - RSVPreF vaccine powder and solvent for solution for intramuscular injection

• **60 microg** of F antigen from RSV subgroup A + **60 microg** of F antigen from RSV subgroup B. Once reconstituted, the vial contains one 0.5-ml dose, to be drawn up into the syringe.

Pfizer

■ RSV vaccine without adjuvant

■ **New indication:** "active immunisation of individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by respiratory syncytial virus". [EU centralised procedure]

■ **Dosage:** "a single dose of 0.5 ml".

In adults aged 60 years or older, respiratory syncytial virus (RSV) infections mainly present as acute respiratory infections, with no specific clinical signs. In some cases, these infections develop into respiratory distress and can even be fatal. The risk factors for developing severe RSV infection are: advanced age; tobacco exposure; pre-existing conditions such as congestive heart failure, chronic obstructive pulmonary disease and asthma; and immunosuppression (see "RSVPreF3/AS01_E vaccine (Arexvy®) in the prevention of RSV infections from 60 years of age", pp. 5-8).

Prevention of RSV infections is mainly based on general measures designed to reduce the spread of the viruses that cause respiratory infections, in particular frequent handwashing, and in some cases wearing a mask. In adults aged 60 years or older, the RSVPreF3/AS01_E vaccine (an adjuvanted RSV vaccine) reduced the risk of RSV-associated lower respiratory tract infection by 83% (0.05% of reported cases in the vaccine group versus 0.3% in the placebo group). This vaccine has not been shown to constitute a therapeutic advance due to uncertainties about its efficacy in preventing severe infections, in particular in those at highest risk, and due to possible increased incidence of immune disorders and atrial fibrillation.

In the European Union, the RSVPreF vaccine was already authorised for use during pregnancy to prevent RSV infection in the woman's child after birth. It has also been authorised in adults aged 60 years or older (1,2).

In this situation, the clinical evaluation of the RSVPreF vaccine is mainly based on a double-blind randomised placebo-controlled trial. This trial was conducted in 7 countries in both the northern and southern hemispheres. It included 34 284 adults aged 60 years or older, who received a single intramuscular injection of either the RSVPreF vaccine or placebo. Immunocompromised persons were excluded from the trial (2,3).

MARKETING AUTHORISATIONS

At baseline, half the participants were aged 67 years or older, and about 6% were aged 80 years or older. About 15% of participants had a chronic cardiac or respiratory condition (2,3).

A trial in 34 000 people, but very few reported RSV infections. Half of the participants were followed up for at least 7 months. The preventive efficacy of the vaccine was evaluated based on the number of people with an RSV-associated lower respiratory tract infection, defined by the presence of at least 2 signs or symptoms of lower respiratory tract disease (such as cough, dyspnoea, wheezing or increased respiratory rate), alongside laboratory confirmation of the infection by RT-PCR (reverse transcriptase polymerase chain reaction) testing. From day 15 after the injection onwards, 11 people (0.07%) had an infection of this type in the vaccine group versus 33 (0.2%) in the placebo group, representing a statistically significant reduction in the relative risk of RSV-associated lower respiratory tract infection of about 67%. The confidence interval for this result, defined in the protocol as 96.66%, was very broad (29% to 86%), reflecting a high degree of uncertainty about the level of this efficacy. According to a press release from the pharmaceutical company, during a second consecutive RSV season, the efficacy of the vaccine was comparable to that during the first season, without a booster dose (2-4).

In adults aged 80 years or older, the reduction in the risk of RSV-associated lower respiratory tract infections was not statistically significant in the vaccine group, possibly due to insufficient statistical power given the small number of trial participants from this age group (2,3).

2 cases of severe infection (defined as resulting in hospitalisation, oxygen supplementation or mechanical ventilation) were reported, both in the placebo group, which is not sufficient to demonstrate the efficacy of the vaccine in preventing severe infections (2,3).

Mortality was 0.3% in both groups. The documentation from the European and US drug regulatory agencies (the European Medicines Agency [EMA] and the Food and Drug Administration [FDA]) do not specify whether any of these deaths were related to RSV infection (2,3).

Adverse effects common to all vaccines, including Guillain-Barré syndrome and possibly an increased incidence of atrial fibrillation. The known adverse effects of the *RSVpreF* vaccine mainly consist of injection-site reactions and systemic reactions. In the trial in adults aged 60 years or older, 3 serious adverse events assessed by the investigators as being related to the vaccine were reported: 2 cases of Guillain-Barré syndrome or a related syndrome, and 1 hypersensitivity reaction. 1 case of sensory-motor polyneuropathy was reported after the data cut-off date: according to the FDA, a causal association with administration of this vaccine cannot be ruled out (1-3).

Cardiac arrhythmias were reported more frequently in the vaccine group: 21 cases (0.1%) versus 8 cases (about 0.05%) in the placebo group. Most of these were cases of atrial fibrillation: 10 cases (4 serious) in the vaccine group versus 4 cases (3 serious) in the placebo group. A causal association with the vaccination has not been ruled out, particularly since in a trial of the *RSVpreF3/AS01_e* vaccine, atrial fibrillation also appeared to be more common in the vaccine group than in the placebo group (see “*RSVpreF3/AS01_e* vaccine (Arevvy[®]) in the prevention of RSV infections from 60 years of age” pp. 5-8) (3).

In a randomised trial in adults aged 65 years or older, the *RSVpreF* vaccine was administered either concomitantly with, or separately from, a seasonal flu vaccine. In this trial, immune responses to RSV and the flu virus were weaker when both vaccines were administered at the same time. The clinical consequences of these weaker immune responses are unknown. Despite the reassurance given in the European summary of product characteristics (SmPC), it is therefore advisable to avoid concomitant administration of these two vaccines (2).

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Literature search up to 24 June 2024



In response to our request for information, Pfizer sent us published documents.

- 1- Prescrire Editorial Staff “RSVpreF vaccine (Abrysvo[®]) during pregnancy to prevent RSV infection in the woman’s child after birth. Fewer severe infections and hospitalisations, but more preterm births and many unknowns” *Prescrire Int* 2024; **33** (258): 89-92.
- 2- EMA - CHMP “Public assessment report for Abrysvo. EMEA/H/C/006027/0000” 20 July 2023: 151 pages.
- 3- US FDA - CDER “Application number STN125769/0. Clinical review memorandum” 31 May 2023: 69 pages.
- 4- Pfizer “Pfizer announces positive top-line data for full season two efficacy of ABRYSVO for RSV in older adults” 29 February 2024: 6 pages.

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Other news

Common Sense Oncology principles for the design, analysis, and reporting of phase 3 randomised clinical trials

Gyawali, Bishal et al., *The Lancet Oncology*, Volume 26, Issue 2, e80 - e89

DOI: 10.1016/S1470-2045(24)00451-0

Summary

Common Sense Oncology (CSO) prioritises treatments providing meaningful benefits for people with cancer. Here, a description of CSO principles aimed at improving the design, analysis, and reporting of randomised, controlled, phase 3 clinical trials evaluating cancer treatments. These principles include: (1) control treatment should be the best current standard of care; (2) the preferred primary endpoint is overall survival or a validated surrogate; (3) an absolute measure of benefit should be provided, such as the difference between groups in median overall survival times or the proportion of surviving patients at a prespecified time; (4) health-related quality of life should be

at least a secondary endpoint; (5) toxicity should be described objectively without subjective language diminishing its importance; (6) trials should be designed to show or rule out clinically meaningful differences in outcomes, rather than a statistically significant difference alone; (7) censoring should be detailed, and sensitivity analyses done to determine its possible effects; (8) experimental treatments known to improve overall survival at later disease stages should be offered and funded for patients progressing in the control group; and (9) reports of trials should include a lay-language summary. Checklists are included to guide compliance with these principles. By encouraging adherence, CSO aims to ensure that clinical trials yield results that are scientifically robust and meaningful to patients.

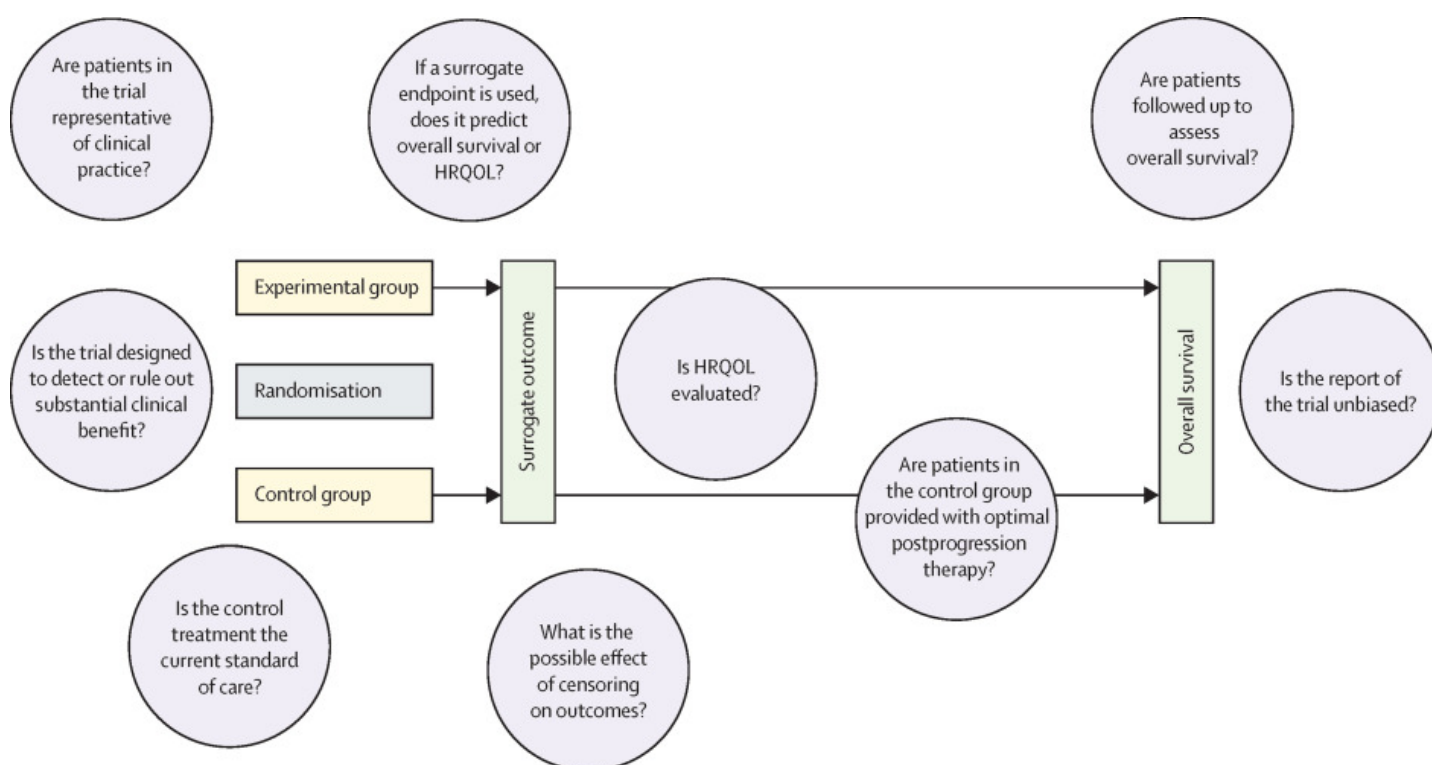


Figure: Questions relating to the design and reporting of randomized controlled trials
Figure adapted from Gyawali and colleagues. HRQOL=health-related quality of life

A checklist for the design of RCTs that evaluate new systemic therapies for cancer

- The control group should receive the current best standard-of-care therapy that is available at the time that the trial is initiated
- Eligibility criteria should not be overly restrictive for easier translation to everyday practice
- The preferred primary endpoint for most RCTs is overall survival; if a potential surrogate endpoint is used, evidence of surrogacy for overall survival or HRQOL should be provided
- A validated measure of HRQOL should be at least a secondary endpoint in RCTs evaluating treatments for cancer
- Participants should be followed up long enough to assess overall survival, irrespective of the primary endpoint; patients should be asked during the trial for permission to collect follow-up data about treatment and survival after the closure of the trial
- Sample size and statistical design of RCTs should be based on their ability to show or rule out differences that meet thresholds for meaningful benefit, such as those of the European Society of Medical Oncology's Magnitude of Clinical Benefit Scale; trials that do not meet those criteria should be reported as not showing meaningful benefit
- Toxicity should be evaluated objectively, including interruption or discontinuation of treatment, chronic lower grade toxicity, and time toxicity; patient reporting of toxicity is encouraged
- Measures should be taken to minimise drop-out and loss to follow-up of patients; permission should be sought at the time of recruitment to obtain information about their status in the absence of following trial procedures
- Sensitivity analyses to determine the potential effect of censoring on trial results should be described in the protocol
- Any subgroup analyses based on biomarkers should be defined in the protocol
- RCTs evaluating earlier treatment shown to improve overall survival for patients with late-stage disease should provide that treatment to patients in the control group at time of disease progression, if they are fit enough to receive it, and it should be funded by the sponsor

RCT= randomised controlled trial. HRQOL=health-related quality of life.

A checklist for reporting of randomised controlled trials that evaluate systemic therapies

- The abstract should contain:
 - An explicit definition of the primary endpoint
 - The hazard ratio for the primary time-to-event endpoint and for overall survival, with CIs and a measure of absolute benefit, even if data for overall survival are immature
 - An objective summary of grade 3-5 toxicity, time lived

with chronic toxicities, and treatment discontinuation, without subjective terms lessening toxicity

– A statement about effect on HRQOL

- There should be a summary of the main results written in language understandable to patients
- The methods section should contain:
 - A statement as to how patients or the public were involved in the study design and approval
 - Justification of the control group, which should be the current standard of care
 - Justification of the primary endpoint and, if not overall survival, evidence of surrogacy for overall survival or HRQOL
 - The statistical basis for the sample size, and for the level of benefit that the trial is powered to detect or exclude
 - Strategies to reduce drop-out and censoring
 - Plans for crossover, and indication whether crossover to the experimental treatment is mandated and funded
 - Criteria for interim analysis and early stopping, with indication that palliative trials should only be stopped early if there is a definitive improvement in overall survival
- The results section should contain:
 - Time-to-event curves for the primary endpoint and for overall survival (if not the primary endpoint), with numbers at risk and numbers censored below the curves
 - An absolute measure of benefit
 - Reasons for drop-out and censoring, with sensitivity analysis to determine potential effects on the main result (can be in an online [appendix](#))
 - Numbers of patients in the control group who crossed over to receive the experimental treatment after disease progression; postprogression treatments for all patients
 - Objective assessment of toxicity, with patient assessment of toxicity encouraged
 - Statement as to whether the trial meets the pre-planned European Society for Medical Oncology Magnitude of Clinical Benefit Scale criterion of benefit, with a statement that results are negative if it does not, regardless of the p value
 - Inclusion of time-toxicity if the expected median overall survival is less than 12 months
- The discussion section should contain:
 - A summary of the main results
 - For a comprehensive risk-benefit assessment, all types of toxicities (eg, physical, financial, and time) should be discussed
- Drafting of the manuscript by a medical writer employed by or contracted to the sponsor is discouraged
HRQOL=health-related quality of life.