News from the EMA

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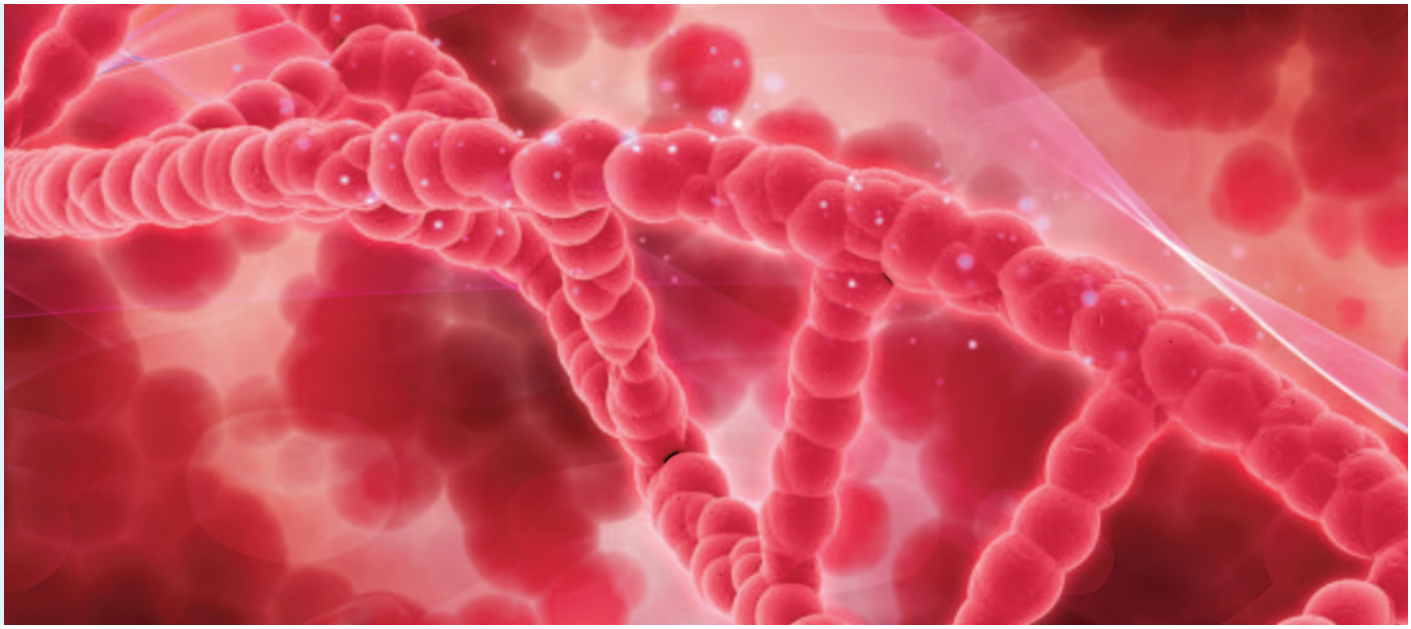


Photo: Freepik

EMA recommends revocation of authorisation for sickle cell disease medicine Adakveo

May 26, 2023

EMA's Committee for Medicinal Products for Human Use (CHMP) has recommended revoking the marketing authorisation for Adakveo (crizanlizumab), a medicine for preventing painful crises (called vaso-occlusive crises) in patients aged 16 years and older with sickle cell disease. The sickle cell disease is a genetic condition in which the red blood cells become rigid and sticky and change from being disc-shaped to being crescent-shaped (like a sickle). These cells can block the blood flow in blood vessels, causing painful crises that affect the chest, abdomen, and other parts of the body.

The active substance in Adakveo, crizanlizumab, is a monoclonal antibody designed to attach to a substance, P-selectin, present on the surface of the cells lining blood vessels. P-selectin helps cells stick to the blood vessels and plays a role in the clogging up of vessels during painful crises in sickle cell disease. By attaching to and blocking the action of P-selectin, the medicine helps prevent painful crises.

The CHMP reviewed results of the STAND study, which compared the effectiveness and safety of Adakveo with placebo (a dummy treatment) in patients who had previously had painful crises leading to a healthcare visit. The study showed that Adakveo did not reduce the number of painful crises leading to a healthcare visit. Patients treated with Adakveo had on average 2.5 painful crises with a subsequent healthcare visit over the first year of treatment, compared with 2.3 crises in the placebo group. In addition, the average number of crises requiring a healthcare visit or treatment at home was 4.7 with Adakveo compared with 3.9 with placebo.

In its review, the CHMP also looked at data from other studies, a managed access programme and real-world data. However, those studies had several limitations, such as the lack of a comparator, and could not be used to show the effect of Adakveo or counterbalance the negative results of the STAND study. In terms of safety, the STAND study did not raise new concerns but showed a higher rate of severe and serious treatment-related side effects for Adakveo compared with placebo. The CHMP therefore concluded that its benefits do not outweigh the risks.

At the time of marketing authorisation, data showed that Adakveo was effective at reducing the number of painful crises in patients with sickle cell disease. However, the data were limited and there was some uncertainty about the size of the medicine's effect. EMA therefore requested the STAND study as a condition for the marketing authorisation of Adakveo, which was granted in October 2020. As the STAND study results do not confirm the benefits previously seen with Adakveo, the CHMP has now concluded that the benefits do not outweigh the risks and recommended the revocation of its authorisation in the EU. The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

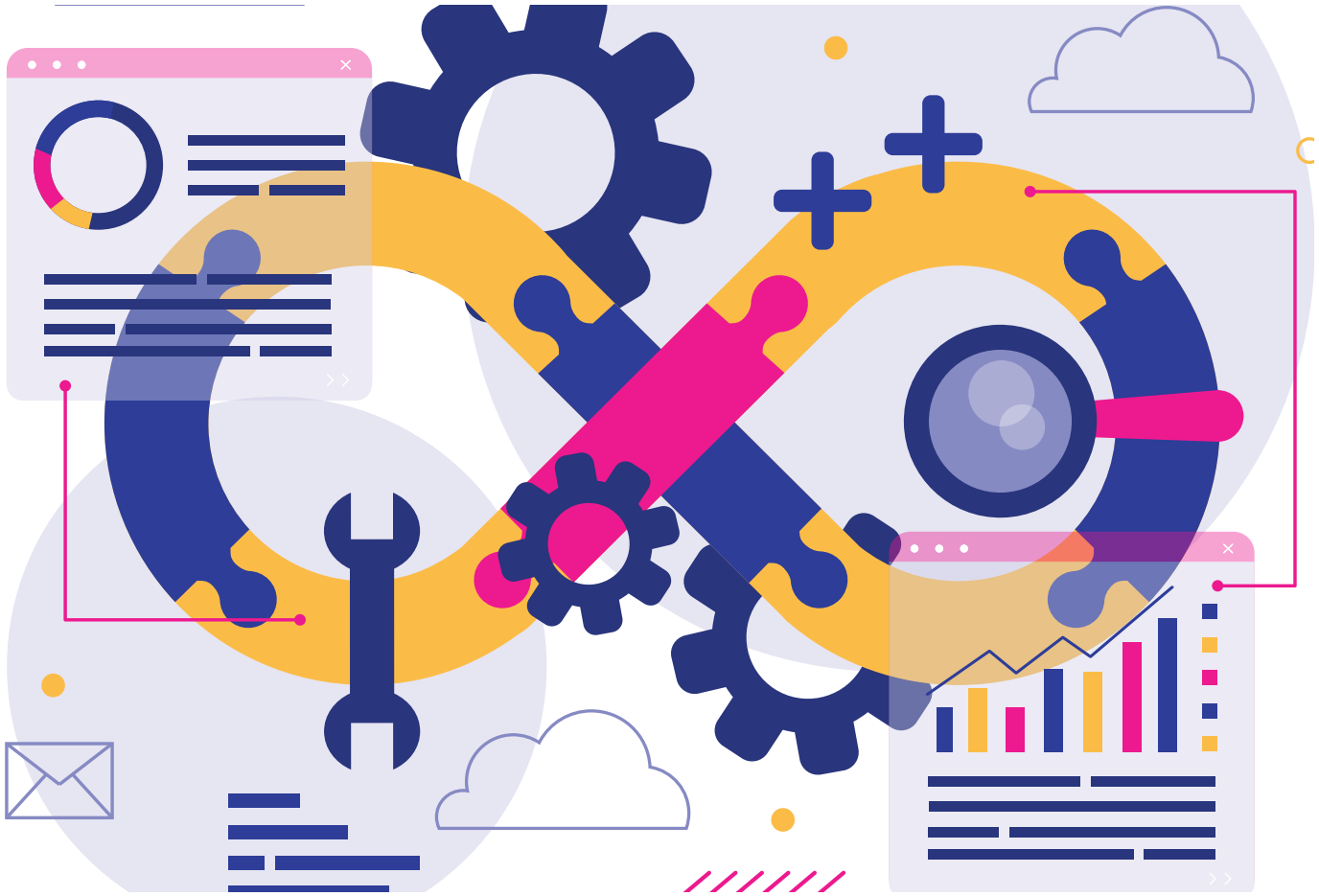


Photo: Freepik

OPEN framework extended to a wider range of medicines

July 20, 2023

EMA has expanded the scope of the OPEN initiative from COVID-19 vaccines and treatments to a wider range of medicines, such as medicines with the potential to address antimicrobial resistance (AMR), respiratory syncytial virus (RSV) infections, or newly diagnosed myelodysplastic syndromes (and other hereditary diseases).

OPEN was established by EMA in December 2020 as a framework to increase international collaboration and share scientific expertise on the evaluation of COVID-19 vaccines and therapeutics, initially as a pilot. All COVID-19 vaccines and therapeutics evaluated since the launch of the pilot were assessed under the OPEN framework. Participating non-EU experts attended and contributed to CHMP and EMA's Emergency Task Force (ETF) evaluations. OPEN allows regulators from Australia, Brazil, Canada, Japan, Switzerland, and the WHO to conduct near-concurrent reviews of certain new medicines and exchange their views and reports on the product assessments. This can help accelerate and align regulatory decisions in several regions in the world, leading to fewer questions for industry and more alignment on the product labelling, while maintaining regulators' independence in their decision making. The extension of the OPEN framework is based on the positive findings and recommendations highlighted in the report on the OPEN pilot.

The collaboration with WHO means that OPEN can also accelerate regulatory decisions and availability of medicines in low- and middle-income countries. Following the success of the pilot, the Agency's Management Board endorsed the expansion of the initiative in March 2022. The new extended scope of OPEN includes marketing authorisation applications for:

- medicines targeting AMR;
- medicines supported through EMA's PRIority MEdicines (PRIME) scheme, but currently not including advanced therapy medicinal products (ATMPs);
- medicines with the potential to address RSV infections or newly diagnosed myelodysplastic syndromes and other hereditary diseases; and
- medicines responding to health threats or public health emergencies.

The first product currently being assessed under the new OPEN framework is an mRNA vaccine against RSV, together with Swissmedic. Discussions are ongoing with OPEN partners on the selection of other products to be included in the OPEN framework. Medicines eligible for assessment under OPEN require CHMP and at least one OPEN partner to agree to conduct parallel assessments.

The dossier content/claimed indication and timing of submissions to both EMA and the OPEN partner(s) should also be aligned. The Agency will engage regularly with stakeholders as more experience is gained. Medicines assessed under OPEN will be clearly labelled in publicly available CHMP agendas and minutes, and on EMA's website. Further information is available in the updated Q&A document. EMA has bilateral agreements with all regulatory authorities involved in OPEN. Standard EMA requirements for EU experts participating in the assessment of medicines (e.g., confidentiality and absence of conflicts of interest) also apply to OPEN experts.

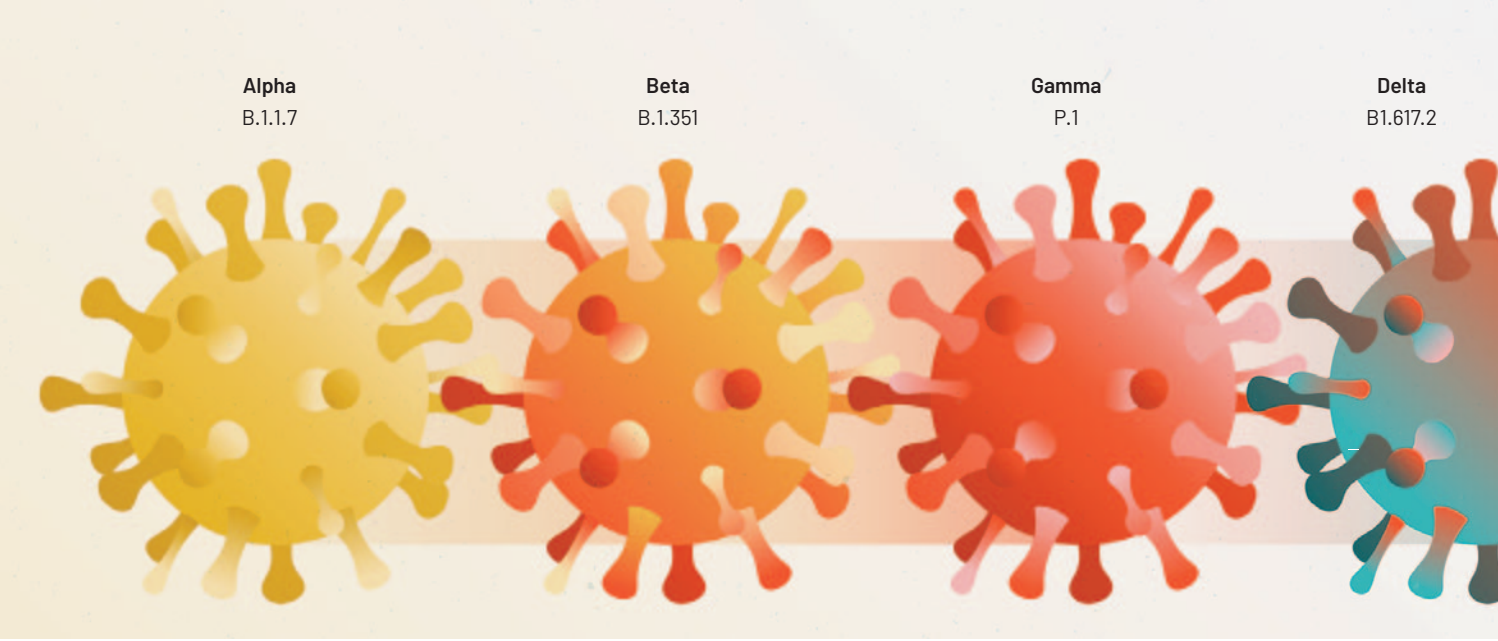
Global regulators agree on way forward to adapt COVID-19 vaccines to emerging variants

May 30, 2023

International regulators have published a report today highlighting the outcomes of their discussions on COVID-19 vaccines and the need for and strategy to update their composition based on the emerging evidence on coronavirus SARS-CoV-2 variants and lessons learned from previous vaccine updates. The workshop, co-chaired by the EMA and the US Food and Drug Administration (FDA), was organised under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA) and took place on May 8, 2023.

Currently authorised vaccines continue to be effective at preventing hospitalisation, severe disease and death due to COVID-19. However, protection against infection wanes over time and as new SARS-CoV-2 variants emerge. Preliminary data show that COVID-19 vaccines adapted to the currently circulating strains improve immunity to recently emerged variants, such as XBB descendent lineages.

Meeting participants discussed the available scientific evidence on epidemiology, seroprevalence (i.e., the number of persons in a population who test positive for a specific disease based on blood serum measurements) and vaccine performance, and key regulatory considerations related to the adaptation of authorised or new COVID-19 vaccines against emerging coronavirus variants. There is a broad agreement that vaccine formulations for the upcoming winter season in the northern hemisphere should include only one virus strain and be based on the XBB family of Omicron subvariants (such as XBB.1.5). International regulators also highlighted that such monovalent vaccines could be used for both booster and primary vaccinations (the latter, for example, only in young children



Phasing out of extraordinary COVID-19 regulatory flexibilities

July 6, 2023

EMA, the European Commission (EC) and the Heads of Medicines Agencies (HMA) are phasing out the extraordinary regulatory flexibilities for medicines put in place during the COVID-19 pandemic to help address regulatory and supply challenges arising from the pandemic. This follows the end of the COVID-19 public health emergency declared by WHO in May 2023.

The extraordinary regulatory flexibilities covered different areas, including marketing authorisation and related regulatory procedures, manufacturing, and importation of active pharmaceutical ingredients and finished products, quality variations, labelling and packaging requirements, and compliance. The EC, HMA, and EMA also agreed during the pandemic on a series of measures to mitigate the impact of disruptions caused by the public health emergency on inspections of manufacturing facilities or other sites relevant for medicinal products in the EU. The extraordinary flexibilities ensured the continued availability of medicines while making sure that good manufacturing (GMP) and distribution practice (GDP) standards were being adhered to.

From now on, the regulatory flexibilities that were introduced jointly by the HMA, EC, and EMA specifically during the COVID-19 pandemic should no longer be granted. For already approved labelling flexibilities, e.g., the English-only labelling for COVID-19 vaccines, their application will be extended until the end of 2023, in order to ensure a smooth phase-out and avoid any supply difficulties or other disruptions due to a sudden change in applicable requirements. After 2023, the regular mechanisms foreseen in the legislation in relation to labelling exemptions should be followed.

Concerning on-site GMP and GDP inspections, these have been restarted after being postponed or carried out remotely during the pandemic; however, a considerable number of postponed inspections still need to be carried out. The validity of GMP and GDP certificates has

below 4 to 5 years of age). They noted that only data on manufacturing and quality of the vaccine and laboratory data would be required for the authorisation or approval of strain changes for the already authorised COVID-19 vaccines, provided that post-authorisation data regarding vaccine quality, effectiveness, immunogenicity, and safety data are collected.

The meeting built on the experience and knowledge gained from a series of ICMRA workshops on COVID-19 vaccine development and virus variants held over the past three years. Participants included representatives of international regulators as well as experts from the World Health Organization (WHO).

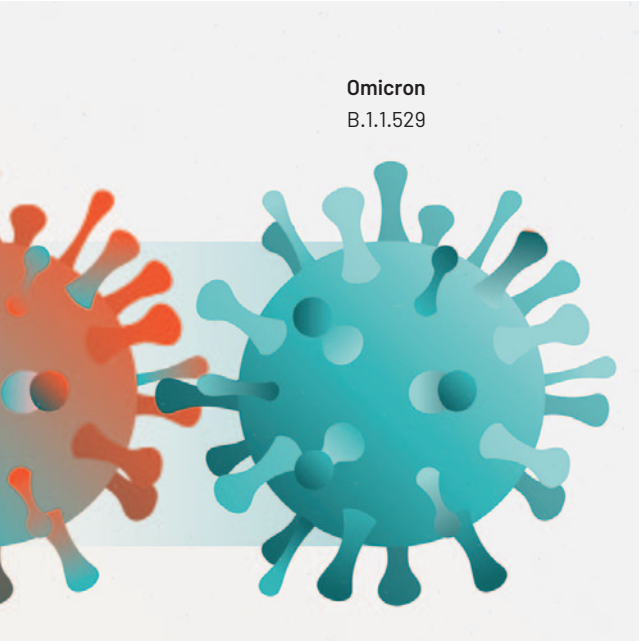


Photo: Freepik

currently been extended until the end of 2023, and the GMDP Inspectors Working Group will issue in the coming months an update on the approach for 2024. This Group has also reviewed experiences with remote working arrangements of Qualified Persons during the pandemic, and will issue guidance on how those specific arrangements can be applied in the future.

Experiences gathered during the application of the COVID-19 regulatory flexibilities are being collected by EMA's Executive Steering Group on Shortages and Safety of Medicinal Products (MSSG). They will consider how lessons learned can inform best practices for tackling medicine shortages in case of new and emerging health challenges in the future.

Reflection paper on the use of artificial intelligence in the lifecycle of medicines

July 19, 2023

EMA has published a draft reflection paper outlining the current thinking on the use of artificial intelligence (AI) to support the safe and effective development, regulation, and use of human and veterinary medicines. This paper, which is now open for public consultation, reflects on principles relevant to the application of AI and machine learning (ML) at any step of a medicines' lifecycle, from drug discovery to the post-authorisation setting.

The reflection paper is part of the joint HMA-EMA Big Data Steering Group (BDSG) initiatives to develop the European Medicines Regulatory Network's capability in data-driven regulation. It has been developed in liaison between the BDSG, EMA's CHMP, and its Committee for Veterinary Medicinal Products (CVMP). The HMA is a network of the heads of the National Competent Authorities (NCA) whose organisations are responsible for the regulation of medicinal products for human and veterinary use in the European Economic Area. The HMA co-operates with the EMA and the European Commission in the operation of the European medicines regulatory network.

AI and ML tools have the potential to effectively support the acquisition, transformation, analysis, and interpretation of data across the medicinal product lifecycle. Their application can include, for example, AI/ML modelling approaches to replace, reduce, and refine the use of animal models during the preclinical development. In clinical trials, AI/ML systems may support the selection of patients based on certain disease characteristics or other clinical parameters; AI/ML tools can also support data recording and analyses which will in turn be submitted to regulators in marketing-authorisation procedures. At the marketing-authorisation stage, AI applications include tools to draft, compile, translate, or review data to be included in the product information of a medicine. In the post-authorisation phase, such tools can effectively support, for example, pharmacovigilance activities including adverse event report management and signal detection.

This range of applications brings with it challenges such as the understanding of the algorithms, notably their design and possible biases, as well as the risks of technical failures and the wider impact these would have on AI uptake in medicine development and health. The reflection paper highlights that a human-centric approach should guide all development and deployment of AI and ML. The use of AI in the medicinal product lifecycle should always occur in compliance with the existing legal requirements, consider ethics, and ensure due respect of fundamental rights. If an AI/ML system is used in the context of medicines' development, evaluation, or monitoring, and is expected to impact on the benefit-risk balance of a medicine, EMA advises developers to seek early regulatory support, e.g., through qualification of innovative development methods (for human medicines) or scientific advice.

All interested stakeholders are invited to comment on the draft reflection paper and to identify opportunities and risks of AI in the field of medicines. The public consultation is open until December 32, 2023, and the topic will be further discussed during a joint HMA/EMA workshop scheduled for November 20-21, 2023. The feedback from stakeholders will be analysed and considered for the finalisation of the reflection paper and future development of guidance as relevant.

First RSV vaccine to protect infants up to 6 months of age and older adults

July 21, 2023

EMA has recommended granting a marketing authorisation in the European Union (EU) for Abrysvo, a vaccine to protect against disease caused by the respiratory syncytial virus (RSV). Abrysvo is the first RSV vaccine indicated for passive immunisation of infants from birth through 6 months of age following administration of the vaccine to the mother during pregnancy. This vaccine is also indicated for active immunisation of adults aged 60 years and older.

RSV is a common respiratory virus that usually causes mild, cold-like symptoms but it can cause serious consequences for children and older adults. In fact, in children RSV is a leading cause of paediatric hospitalisation in Europe. It may cause bronchiolitis and pneumonia and can lead to fatal respiratory distress. RSV infection can also be serious for adults aged 50 years and older as it can cause acute respiratory infection, influenza-like illness, or community-acquired pneumonia.

Abrysvo is a bivalent vaccine composed of two recombinant RSV fusion surface glycoproteins selected to optimise protection against RSV A and B strains. These proteins are essential for RSV to infect the body and are also the main targets of the antibodies generated to fight the infection.

Abrysvo was evaluated under EMA's accelerated assessment mechanism because prevention of RSV disease is considered to be of major public health interest. When a person is given the vaccine, their immune system generates specific antibodies and T cells (immune system cells) that help prevent RSV infection. In case of pregnant individuals, the neutralising antibodies cross the placenta, providing infants with protection up to 6 months after birth.

The opinion by EMA's CHMP is based on data from two randomised, placebo-controlled, pivotal studies. In one study, 3,695 women at 24-36 weeks of pregnancy were administered Abrysvo while 3,697 received a placebo (dummy injection). The assessment showed that the vaccine was effective in reducing both severe medically attended lower respiratory tract illness and medically attended lower respiratory tract illness occurring within 180 days after birth.

In the other study, 18,488 adults aged 60 years and older were administered the vaccine, while 18,479 received a placebo. The results of the study demonstrated efficacy for Abrysvo in the reduction of RSV-associated lower respiratory tract illness with 2 (or more) symptoms and with 3 (or more) symptoms.

The most common side effects reported in individuals between 24 and 36 weeks of pregnancy were vaccination site pain, headache, and muscle pain. In individuals 60 years of age and older the most frequently reported side effect was vaccination site pain.

The opinion adopted by the CHMP is an intermediary step on Abrysvo's path to patient access. The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.