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Public summary of the evaluation of a proposed paediatric investigation plan

Covalently closed DNA plasmids coding for cytomegalovirus phosphoprotein 65 and glycoprotein B genes for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity

On 14 November 2014, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for covalently closed DNA plasmids coding for cytomegalovirus phosphoprotein 65 and glycoprotein B genes for the prevention of cytomegalovirus disease in patients with impaired cell-mediated immunity (EMA-001612-PIP01-14).

What is covalently closed DNA plasmids coding for cytomegalovirus phosphoprotein 65 and glycoprotein B genes, and how is it expected to work?

Covalently closed DNA plasmids coding for cytomegalovirus phosphoprotein 65 and glycoprotein B genes (hereafter referred to as ASP0113) is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the 'Prevention of CMV disease and associated complications in at risk CMV-seropositive recipient (R+) patients who have undergone hematopoietic stem cell transplantation (HCT) using either CMV-seropositive donors (D+) or CMV seronegative donors (D-)' and for the 'Prevention of CMV disease and associated complications in at risk patients who have undergone solid organ transplantation (SOT) using D+/ CMV-seronegative recipients (R-), D+/R+ or D-/R+'.

Cytomegalovirus (CMV) is a common virus that normally causes a mild infection such as a sore throat. Most people get infected at some stage during their lifetime. After infection, the virus remains in the body in a 'latent' (inactive) state and is kept under control by the immune system, in particular its cell-mediated immunity (a defence mechanism whereby specialised cells called T lymphocytes directly neutralise viruses). In people with weakened cell-mediated immunity, such as transplant patients receiving immunosuppressant treatment (medicines that reduce the activity of the immune system to prevent rejection of the graft), CMV can become active again and, this time, cause severe infection.

ASP0113 is a vaccine. Vaccines work by 'teaching' the immune system how to defend itself against a disease. ASP0113 contains the genes responsible for making two proteins of CMV (phosphoprotein 65 and glycoprotein B). When given to the patient, the genes are expected to produce the two proteins, which are in turn expected to stimulate an immune response against CMV. The immune system is then



expected to be able to produce a more effective response when it is exposed to the virus again, such as when latent virus becomes reactivated in a transplant patient on immunosuppressant therapy.

What was the proposal from the applicant?

For children, the applicant proposed:

To study the vaccine in a paediatric investigation plan* in children from birth to less than 18 years of age who have received a solid organ transplant, and in children from 2 years to less than 18 years of age who have received a haematopoietic stem cell transplant. These children are at risk of CMV infection due to the immunosuppressant treatment they are receiving. The future indication proposed for children is: 'Prevention of cytomegalovirus disease and associated complications in hematopoietic stem cell transplantation (HCT) and solid organ transplantation (SOT) recipients'. The plan includes a proposal to show safety and immunogenicity of the vaccine in clinical studies. The applicant proposed a deferral* for the paediatric clinical studies.

Is there a need to treat children at risk of CMV disease?

Taking into account the proposed indication in adults, and the characteristics of the vaccine, the Paediatric Committee considered this vaccine of potential use for the prevention of cytomegalovirus disease in patients at risk. Solid organ and haematopoietic stem cell transplants are also performed in children of all ages, and like adults, these children can be at risk of CMV disease due to the immunosuppressant treatment they are receiving to prevent graft rejection. The Paediatric Committee also noted that haematopoietic stem cell transplants are sometimes performed in children less than 2 years of age, albeit very rarely. Nonetheless, the Committee was of the opinion that these children should not be excluded from the clinical development, as initially proposed by the applicant.

What did the Paediatric Committee conclude on the potential use of this medicine in children?

At present, no vaccine for the prevention of CMV disease is authorised in the European Union. Therefore, the Committee considered that data are required to decide whether the use of this vaccine will bring a benefit to the children at risk of CMV disease, and to understand any potential risks.

The Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- It is necessary to study immunogenicity, i.e. if the vaccine is effective in stimulating an immune response. This will be done in two studies, one in haematopoietic stem cell transplant recipients, and one in solid organ transplant recipients.
- While it is necessary to study vaccine efficacy, i.e. if the vaccine is effective in preventing CMV disease, this cannot be studied directly in children, as CMV disease occurs only very rarely and large studies would be required, which cannot be practically performed in children. Therefore, efficacy in preventing CMV disease may be extrapolated from adults based on immunogenicity and/or the effects of the vaccine on the 'viral load' (the amount of CMV in the blood), provided the adult clinical development programme identifies a vaccine response that correlates with protection from CMV disease.

- It is necessary to study the potential side effects of the vaccine, to prevent them or to reduce the consequences if they occur. Safety and reactogenicity of the vaccine are being investigated in the two paediatric studies.
- As solid organ and haematopoietic stem cell transplants are sometimes performed also in neonates, the two clinical studies will include children from birth.

What happens next?

The applicant has now received the EMA Decision (P/0338/2014)* on this medicine. The Decision itself is necessary for the applicant to request in the future a marketing authorisation* for this medicine in adults and/or in children*.

The Decision* on the agreed Paediatric Investigation Plan means that the applicant is bound to perform the studies and trials with children in the next months or years. In case of difficulties, or a change in current knowledge or availability of new data, the applicant may request changes to the plan at a later stage. This can be done through a modification of the PIP.

The agreed completion of all the studies and trials included in the Paediatric Investigation Plan is December 2026.

Trials in the Paediatric Investigation Plan will be listed in the public EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>) as soon as they have been authorised to be started, and their results will have to be listed in the register within 6 months after they have completed.

The results of the studies conducted in accordance with the agreed Paediatric Investigation Plan will be assessed, and any relevant information will be included in the Product Information (summary of product characteristics, package leaflet). If the medicine proves to be effective and safe to use in children, it can be authorised for paediatric use, with appropriate recommendations on the dose and on necessary precautions. The product information will also describe which adverse effects are expected with the medicine, and wherever possible, how to prevent or reduce these effects.

***Definitions:**

Applicant	The pharmaceutical company or person proposing the Paediatric Investigation Plan or requesting the Product-Specific Waiver
Children	All children, from birth to the day of the 18 th birthday.
Paediatric investigation plan (PIP)	Set of studies and measures, usually including clinical studies in children, to evaluate the benefits and the risks of the use of a medicine in children, for a given disease or condition. A PIP may include "partial" waivers (for example, for younger children) and/or a deferral (see below).
Waiver	An exemption from conducting studies in children, for a given disease or condition. This can be granted for all children (product-specific waiver), or in specific subsets (partial waiver): for example, in boys or in children below a given age.
Deferral	The possibility to request marketing authorisation for the use of the medicine in adults, before completing one or more of the studies /measures included in a PIP. The Paediatric Committee may grant a deferral to avoid a delay in the availability of the medicine for adults.
Opinion	The result of the evaluation by the Paediatric Committee of the European Medicines Agency. The opinion may grant a product-specific waiver, or agree a PIP.
Decision	The legal act issued by the European Medicines Agency, which puts into effect the Opinion of the Paediatric Committee.
Pharmaceutical form	The physical aspect of the medicine (the form in which it is presented), for example: a tablet, capsule, powder, solution for injection, etc. A medicine can have more than one pharmaceutical form.
Placebo	A substance that has no therapeutic effect, used as a control in testing new drugs.
Active control	A medicine with therapeutic effect, used as a control in testing new drugs.
Historical control	A group of patients with the same disease, treated in the past and used in a comparison with the patients treated with the new drug.
Route of administration	How a medicine is given to the patient. For example: for oral use, for intramuscular use, for intravenous use, etc. The same medicine, or the same pharmaceutical form, may be given through more than one route of administration.
Patent	A form of protection of intellectual property rights. If a medicinal product is protected by a patent, the patent holder has the sole right to make, use, and sell the product, for a limited period. In certain circumstances, a patent for a medicinal product may be extended for a variable period by a Supplementary Protection Certificate.
Marketing Authorisation	When a Marketing Authorisation is granted, the pharmaceutical company may start selling the medicine in the relevant country (in the whole European Union, if the procedure was a centralised one).