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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

Begelomab for the treatment of acute graft-versus-host disease (aGvHD)

On 11 September 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for begelomab for the treatment of acute graft-versus-host disease (aGvHD) (EMEA-001744-PIP01-14).

What is begelomab, and how is it expected to work?

Begelomab is not authorised in the European Union. Studies in adults have been conducted and a confirmatory study is being planned. This medicine is proposed in adults for the treatment of steroid-resistant aGvHD in patients who underwent allogeneic haematopoietic stem cell transplantation (that is, a transplant from a donor).

GvHD is a complication that can affect patients who have received an allogeneic haematopoietic stem cell transplantation. Allogeneic haematopoietic stem cell transplantation is a complex procedure used to treat diseases such as leukaemia or multiple myeloma (cancers of the white blood cells), whereby a patient receives stem cells from a matched donor to help restore the bone marrow, which produces new blood cells. In GvHD, the transplanted cells recognise the patient as 'foreign' and attack the patient's organs, such as the stomach, gut, skin and liver, leading to organ damage. GvHD can occur shortly after transplantation (acute GvHD), or develop later on (chronic GvHD). GvHD is a serious and life-threatening disease with a high mortality rate.

Initially, aGvHD is usually treated with glucocorticoids, however in some patients the condition is steroid-resistant, meaning it does not respond (sufficiently) to glucocorticoids and second-line therapy is required.

Begelomab is a monoclonal antibody (a type of protein) that has been designed to attach to a receptor called CD26, which is present on the surface of T-cells. These are cells of the immune system that are involved in GvHD. CD26 is responsible for stimulating the T-cells to divide. By attaching to CD26, this medicine is expected to block its activity, reducing the rate at which the T-cells multiply. This is expected to reduce the number of activated T-cells and thereby to lower the risk of these cells attacking the patient's organs.

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What was the proposal from the applicant?

For children, the applicant proposed:

To study the medicine in children from 4 weeks to less than 18 years of age affected by aGvHD, in a paediatric investigation plan*. The future indication proposed for children is: Treatment of steroid-resistant grade II-IV aGvHD after haematopoietic stem cell transplantation or donor lymphocyte infusion. The plan includes a proposal to determine the right dose and to show efficacy and safety of the medicine in clinical studies.

The applicant proposed a deferral* for the paediatric clinical studies.

Is there a need to treat children affected by aGvHD?

Taking into account the proposed indication in adults, and the characteristics of the medicine, the Paediatric Committee considered this medicine of potential use for the treatment of aGvHD. Haematopoietic stem cell transplantations are also performed in children of all ages, who are therefore also at risk of developing aGvHD.

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

At present, no treatment is authorised for the treatment of steroid-resistant aGvHD in children in the European Union. Some treatments are used off-label, but these differ between treatment centres. Therefore, the Committee considered that new data are required to decide whether the use of this medicine will bring a benefit to children from 4 weeks to less than 18 years of age affected by the condition, 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. The Committee therefore agreed with the request of the applicant that the paediatric clinical studies should be deferred.

What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies are not necessary in neonates (from birth to 4 weeks of age) because haematopoietic stem cell transplantation is only very rarely performed in neonates and the time-to-onset in relation to the transplantation means that acute GvHD would only under the most exceptional circumstances occur before 4 weeks of age.
- Further data are required to support the use of the adult pharmaceutical form (a concentrate for solution for infusion) in children.
- Determination of the best dose should be done with a trial of the medicine's behaviour in the body and the body's reactions to it.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in a study comparing the medicine to best second-line therapy as normally used (off-label) at a given study site.
- It is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur. The main concerns identified by the PDCO are the effect of begelomab on the reconstitution of the immune system after transplantation, the risk of relapse due to the

suppression of the graft's activity against the few potentially remaining leukaemia cells (the "graft-versus-leukaemia-effect"), and the potential effects of begelomab on glucose metabolism.

What happens next?

The applicant has now received the EMA Decision (P/0226/2015)* 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 March 2021.

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 18th 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).