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Human Medicines Research and Development Support Division

Public summary of the evaluation of a proposed paediatric investigation plan

(3-((4-Benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) for the treatment of human immunodeficiency virus (HIV-1) infection

On 11 September 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for (3-((4-Benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) (hereafter referred to as BMS-663068) for the treatment of human immunodeficiency virus (HIV-1) infection (EMEA-001687-PIP01-14).

What is BMS-663068, and how is it expected to work?

BMS-663068 is first-in-class of a new type of antiretroviral drugs, i.e. the attachment inhibitors, and blocks the first step of viral entry, namely the attachment of a glycoprotein on the viral envelope (gp120) of the HIV to its receptor on the host T-cell (CD4).

BMS-663068, when taken in combination with other antiretroviral agents, might keep low the amount of HIV at blood level.

BMS-663068 is not authorised in the European Union. Studies in adults are currently on-going. This medicine is proposed in adults for the treatment of HIV-1 infection as part of a combination therapy in adults.

What was the proposal from the applicant?

For children, the applicant proposed to study the medicine in children from 2 years to less than 18 years of age affected by HIV-1 infection, in a paediatric investigation plan*.

The future indication proposed for children is: “treatment of HIV-1 infection as part of a combination therapy in paediatric patients who have no more than two remaining available fully active antiretroviral therapies”. The plan includes the development of specific pharmaceutical forms to be used in children*.

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It also includes a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies and to extrapolate data from studies in adults.

The applicant proposed a deferral* for the development of the specific pharmaceutical forms to be used in children, the paediatric clinical studies and the extrapolation and modelling & simulation studies.

Is there a need to treat children affected by HIV-1 infection?

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 HIV-1 infection. This condition occurs also in children, who can be infected from their mothers at birth. In addition, like adults, adolescents can become infected with HIV e.g. through sexual transmission or through contaminated injection needles.

BMS-663068 is being developed as a later-line alternative for patients whose virus has become resistant to antiretroviral drug classes which are used earlier in the infection. Many children infected at birth start therapy very early in life, and therefore have been exposed to antiretroviral drugs for many years before they reach adulthood. As a result, their virus may have become resistant to some types of antiretroviral drugs before these children reach adulthood, and alternative treatment options are therefore also of interest in children. In addition, already resistant virus can also be transmitted from HIV infected mothers to the baby.

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

At present, several different antiretroviral drug classes are available for the treatment of HIV-1 infection in children in the European Union. However, BMS-663068 is first-in-class in a new antiretroviral drug class, the attachment inhibitors. Therefore, data are required to decide whether the use of this medicine will bring a benefit to children from 2 years to less than 18 years of age affected by the condition, and to understand any potential risks.

The Committee considered that there is also a need to develop specific pharmaceutical forms* of this medicine, which would allow to use the medicine safely and accurately in young children, and whose composition* must only include components that are known to be safe in children.

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:

- Studies are not necessary in children less than 2 years of age, because it is unlikely that the virus in these children has already become resistant to all drug classes which are used earlier in the infection, which would necessitate the use of a later line option such as BMS-663068.
- A pharmaceutical form* was needed for children aged from 2 years to less than 12 years of age. A prolonged-release tablet of an appropriate strength and size, and prolonged-release granules for the youngest children and those unable to swallow tablets will be developed by the applicant. Adolescents from 12 to less than 18 years of age are expected to be able to use the adult prolonged-release tablets.

- Studies in animals need to be performed, to identify any risk before the medicine is used in young children.
- Determination of the best dose should be done with two trials of the medicine's behaviour in the body. In general, for antiretroviral drugs, the 'best dose' in children is the dose producing the same level of drug as the level that has been shown to be safe and effective against the virus in adults, as it is generally expected that a medicine will then also be effective against the virus in children. These assumptions will be confirmed in an extrapolation study. Dose-finding in children will also be supported by modelling & simulation.
- The two trials will also assess the ability of BMS-663068 to suppress HIV replication. Long-term efficacy outcomes particularly in HIV-1 infected young children should be investigated post-authorisation.
- Since it is necessary to study the potential side effects of the medicine, to prevent them or to reduce the consequences if they occur, the two trials will also investigate the safety of BMS-663068.

What happens next?

The applicant has received the EMA Decision (P/0258/2015)* 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 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 February 2024.

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).