09 October 2015
EMA/628991/2015
Human Medicines Research and Development Support Division

# Public summary of the evaluation of a proposed paediatric investigation plan

(4R,5R)-1-[[4-[[4-[3,3-dibutyl-7-(dimethylamino)-2,3,4,5-tetrahydro-4-hydroxy-1,1-dioxido-1-benzothiepin-5-yl]phenoxy]methyl]phenyl]methyl]-4-aza-1-azoniabicyclo[2.2.2]octane chloride **(SHP625)** for the treatment of Alagille syndrome

On 22 May 2015, the Paediatric Committee of the European Medicines Agency agreed a Paediatric Investigation Plan* (PIP) for SHP625 for the treatment of Alagille syndrome (EMEA-001475-PIP02-13).

## What is SHP625, and how is it expected to work?

SHP625 is expected to inhibit bile acid absorption from the gut and increase excretion of bile acids in the faeces of patients with cholestasis (such as those with Alagille syndrome). This medicine is proposed in adults for the treatment of primary biliary cirrhosis and studies in adults and children are currently on-going. SHP625 is not authorised in the European Union.

## What was the proposal from the applicant?

The applicant proposed to study the medicine in children from birth to less than 18 years of age affected by Alagille syndrome, in a paediatric investigation plan*. The future indication proposed for children is: treatment of Alagille syndrome. The plan includes a proposal to determine the right dose and to show efficacy and safety of the medicine in non-clinical and clinical studies.

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

## Is there a need to treat children affected by Alagille syndrome?

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 Alagille syndrome. This is a genetic condition which affects adults and children. The medicine is developed to treat the cholestasis (a symptom) associated with Alagille syndrome.

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

Because there is a need for more medicines for the treatment of Alagille syndrome in children, and this medicine has a potential interest for children, the Committee considered that non-clinical and clinical studies were needed.

However, the Committee considered that it is more prudent to confirm that the medicine is effective and safe in adults, before starting the paediatric studies and agreed with the request of the applicant that paediatric clinical studies should be deferred.

## What is the content of the Plan after evaluation?

The Paediatric Committee considered that:

- Studies in animals need to be performed, to identify any risk before the medicine is used in infants and neonates / young children.
- As Alagille affects neonates as well as older children, 1 clinical study including children from birth to less than 1 year of age will be performed to obtain the necessary data.
- It is necessary to study if the medicine is effective to treat the disease in children. This will be done in 2 studies comparing the medicine to placebo*.
- 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 concern identified by the PDCO is the potential toxicity of the medicine for the brain especially in neonates due to the propylene glycol which is a one of the excipients in the formulation.

## What happens next?

The applicant has now received the EMA Decision (P/0149/2015)* 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 July 2018.

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). |