EMA/643929/2016

European Medicines Agency decision

P/0279/2016

of 7 October 2016

on the acceptance of a modification of an agreed paediatric investigation plan for Eteplirsen (EMEA-001722-PIP01-14-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

Disclaimer

This decision does not constitute entitlement to the rewards and incentives referred to in Title V of Regulation (EC) No 1901/2006.

Only the English text is authentic.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Contact EMA www.ema.europa.eu/contact

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The European Medicines Agency,

Having regard to the Treaty on the Functioning of the European Union,

Having regard to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1],

Having regard to Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[2],

Having regard to the European Medicines Agency's decision P/0029/2016 issued on 29 January 2016,

Having regard to the application submitted by Sarepta International C.V. on 27 June 2016 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 16 September 2016, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

Whereas:

(1) The Paediatric Committee of the European Medicines Agency has given an opinion on the acceptance of changes to the agreed paediatric investigation plan.

(2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for Eteplirsen, concentrate for solution for infusion, age-appropriate dosage form, intravenous use, subcutaneous use are hereby accepted in the scope set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices.

Article 2

This decision is addressed to Sarepta International C.V., Prins Bernhardplein 200, 1097JB – Amsterdam, The Netherlands.

EMA/PDCO/456663/2016

London, 16 September 2016

Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan

EMEA-001722-PIP01-14-M01

Scope of the application

Active substance(s):

Eteplirsen

Condition(s):

Treatment of Duchenne muscular dystrophy

Pharmaceutical form(s):

Concentrate for solution for infusion

Age-appropriate dosage form

Route(s) of administration:

Intravenous use

Subcutaneous use

Name/corporate name of the PIP applicant:

Sarepta International C.V.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Sarepta International C.V. submitted to the European Medicines Agency on 27 June 2016 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0029/2016 issued on 29 January 2016.

The application for modification proposed changes to the agreed paediatric investigation plan.

The procedure started on 19 July 2016.

Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified.

Opinion

1. The Paediatric Committee, having assessed the application in accordance with Article 22 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report

   - to agree to changes to the paediatric investigation plan in the scope set out in the Annex I of this opinion.

   The Norwegian Paediatric Committee member agrees with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the paediatric investigation plan are set out in the Annex I.

This opinion is forwarded to the applicant and the Executive Director of the European Medicines Agency, together with its annex and appendix.

Annex I

The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)

1. Waiver

Not applicable.

2. Paediatric investigation plan

2.1. Condition:

Treatment of Duchenne muscular dystrophy

2.1.1. Indication(s) targeted by the PIP

Treatment of Duchenne muscular dystrophy in paediatric patients amenable to exon 51 skipping

2.1.2. Subset(s) of the paediatric population concerned by the paediatric development

From birth to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Concentrate for solution for infusion Age-appropriate subcutaneous dosage form

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	2	**Study 1** Development of an age-appropriate concentrate for solution for infusion for intravenous use. **Study 2** Development of an age-appropriate dosage form e.g. with an alternative route of administration (such as subcutaneous).
Non-clinical studies	3	**Study 3** Definitive juvenile toxicity study to evaluate the toxicity and toxicokinetics of eteplirsen in male juvenile rats in a 10-week repeat-dose study with a 4-week recovery period. (4658-tox-003) **Study 4** Pharmacokinetic study of eteplirsen in male rats following administration of a single subcutaneous or intravenous dose **Study 5** 12-week subcutaneous toxicity and toxicokinetic study in non human primate

Clinical studies	11	**Study 6** Single blind, placebo-controlled study to evaluate safety, tolerability and activity of eteplirsen (intramuscular) to treat Duchenne muscular dystrophy (DMD) amenable to treatment by exon 51 skipping in male, ambulant or non-ambulant children aged from 10 to less than 17 years. (AVI-4658-33) **Study 7** Open label, multiple-dose, dose ranging study designed to assess the safety, tolerability, pharmacokinetics (PK), and exploratory efficacy of eteplirsen in the treatment of male patients aged from 5 years to less than 15 years with confirmed genotypic DMD amenable to treatment with exon 51 phosphorodiamidate morpholino oligomer (PMO). (AVI-4658-28) **Study 8** Randomised, single centre, double blind, placebo controlled, multiple dose study to assess the efficacy, safety, tolerability, and pharmacokinetics of once weekly intravenous (IV) infusions of eteplirsen in male patients aged from 7 years to less than 14 years with genotypically confirmed DMD amenable to treatment by exon 51 skipping. (4658-us-201) **Study 9** Open-label, non-comparative extension study from study 4658-us-201 to assess long term safety and activity of eteplirsen to treat DMD amenable to treatment by exon 51 skipping in male paediatric patients at two different dose levels. (4658-us-202) **Study 10** Open-label, multi-centre, 96-week study with a concurrent untreated control arm to evaluate the efficacy and safety of eteplirsen in in male patients aged from 7 to less than 17 years with Duchenne muscular dystrophy (DMD). (4658-301) **Study 11** Open-label, non-comparative, multi-centre study to explore the safety and tolerability of eteplirsen in patients aged from 7 to less than 18 years with advanced stage Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. (4658-204) **Study 12** Open-label, multi-centre study to evaluate the safety, tolerability and activity of eteplirsen in patients from 4 to less than 7 years of age with genotypically confirmed DMD with genetic mutations amenable to treatment by exon 51 skipping including evaluation of the natural history in a cohort of untreated patients with DMD not amenable to exon 51 skipping. (4658-203)

		Study 13 Open label, uncontrolled multi-centre, study to assess safety, tolerability and pharmacokinetics, and to explore activity of once weekly intravenous infusions of eteplirsen in patients with genotypically-confirmed Duchenne muscular dystrophy (DMD) with a deletion mutation amenable to exon 51 skipping age 6 months to less than 49 months. (4658-102) **Study 14** Comparative study of the safety, tolerability, and pharmacokinetics of subcutaneous versus intravenous formulations of eteplirsen in adult healthy male subjects. **Study 15** Comparative study of the safety, tolerability, pharmacokinetic, and pharmacodynamic effects of subcutaneous versus intravenous formulations of eteplirsen in paediatric male patients with Duchenne muscular dystrophy amenable to exon 51 skipping therapy aged from 6 months to less than 18 years. **Study 16** Open-label safety, tolerability and pharmacokinetics study of eteplirsen in patients aged from birth to less than 7 months with Duchenne muscular dystrophy amenable to exon 51 Skipping.
Extrapolation, modelling and simulation studies	3	**Study 17** Analysis of existing in-house and literature data on eteplirsen and DMD (amenable to exon 51 skipping therapy) to provide / support efficacy assumptions based on extrapolation of efficacy data of eteplirsen from children aged from 6 years to less than 17 years to children from 4 years to less than 6 years. **Study 18** Analysis of existing in-house and literature data on eteplirsen and DMD (amenable to exon 51 skipping therapy) to provide / support efficacy assumptions in the paediatric population based on extrapolation of efficacy data of eteplirsen for treatment of DMD from children aged from 7 to less than 17 years to children aged from 6 months to less than 5 years. **Study 19** Analysis of existing in-house and literature data on eteplirsen and DMD (amenable to exon 51 skipping therapy) To provide / support efficacy assumptions and dose finding in the paediatric population based on extrapolation of efficacy data for treatment of DMD from children aged 7 to less than 17 years to children from birth to less than 7 months of age.
Other studies	0	Not applicable.

Other measures	0	Not applicable.

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By March 2022
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

6. Reminder

Interventional clinical trials have to be registered with the EudraCT database.

All investigational medicinal products used in the studies or trials must be registered in the EudraVigilance Medicinal Product Dictionary by the sponsor.

Studies or trials which are inconclusive or not interpretable will be considered non-compliant.

The Clinical trials should be performed in accordance with Good Clinical Practice. Those conducted outside the community should be carried out in accordance with the ethical standards of Directive 2001/20/EC and those conducted within the community should be carried out in accordance with Directive 2001/20/EC.

Applicants are reminded that it is their responsibility to submit a request for modification of an agreed paediatric investigation plan, if they encounter difficulties with its implementation which render the plan unworkable or no longer appropriate.

Applicants are also reminded that in order to verify compliance with the agreed PIP, the study report must be submitted for any study that had to be completed (see Commission Guideline 2014/C338/01 of 27 September 2014 and EMA procedural advice). This is part of the validation of the application for marketing authorisation, variation or line extension. Applicants are therefore advised to consider the time necessary to produce the appropriate report for their planned date of submission. For authorised medicinal products, reports need to be submitted to the competent authority within 6 months of completion of the studies, according to article 46 of Regulation (EC) No 1901/2006.