EMA/866546/2015

European Medicines Agency decision

P/0029/2016

of 29 January 2016

on the agreement of a paediatric investigation plan and on the granting of a deferral for eteplirsen (EMEA-001722-PIP01-14) 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 application submitted by Sarepta International C.V. on 10 April 2015 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 11 December 2015, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 of said Regulation,

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 agreement of a paediatric investigation plan and on the granting of a deferral.

(2) It is therefore appropriate to adopt a decision agreeing a paediatric investigation plan.

(3) It is therefore appropriate to adopt a decision granting a deferral.

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

Has adopted this decision:

Article 1

A paediatric investigation plan for eteplirsen, solution for infusion, age-appropriate subcutaneous dosage form, intravenous use, subcutaneous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby agreed.

Article 2

A deferral for eteplirsen, solution for infusion, age-appropriate subcutaneous dosage form, intravenous use, subcutaneous use, the details of which are set out in the opinion of the Paediatric Committee of the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

Article 3

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

Done at London, 29 January 2016

For the European Medicines Agency
Zaïde Frias
Head of Division
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/633031/2015
London, 11 December 2015

Opinion of the Paediatric Committee on the agreement of a Paediatric Investigation Plan and a deferral

EMEA-001722-PIP01-14

Scope of the application

Active substance(s):

Eteplirsen

Condition(s):

Treatment of Duchenne muscular dystrophy

Pharmaceutical form(s):

Solution for infusion

Age-appropriate subcutaneous 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 16(1) of Regulation (EC) No 1901/2006 as amended, Sarepta International C.V. submitted for agreement to the European Medicines Agency on 10 April 2015 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 19 May 2015.

Supplementary information was provided by the applicant on 21 September 2015. The applicant proposed modifications to the paediatric investigation plan and withdrew its request for a waiver.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

Opinion

1. The Paediatric Committee, having assessed the proposed paediatric investigation plan in accordance with Article 17 of Regulation (EC) No 1901/2006 as amended, recommends as set out in the appended summary report:

   - to agree the paediatric investigation plan in accordance with Article 18 of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation.

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

2. The measures and timelines of the agreed 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)

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 solution for injection 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

Area	Number of measures	Description
		Study 5 12-week subcutaneous toxicity and toxicokinetic study in non human primate
Clinical studies	11	**Study 6** Double 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, 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 6 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 patients aged from 7 to less than 14 years at two different dose levels.(4658-us-202) **Study 10** Open-label, multi-centre, 48-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)

Area	Number of measures	Description
		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 4 years. **Study 14** Comparative study of the safety, tolerability, and pharmacokinetics of subcutaneous versus intravenousf 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 6 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

Area	Number of measures	Description
		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