



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/440000/2019

## European Medicines Agency decision P/0286/2019

of 16 August 2019

on the acceptance of a modification of an agreed paediatric investigation plan for eteplirsen, (EMA-001722-PIP01-14-M02) 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.**

---

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Address for visits and deliveries** Refer to [www.ema.europa.eu/how-to-find-us](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European Union



# European Medicines Agency decision

P/0286/2019

of 16 August 2019

on the acceptance of a modification of an agreed paediatric investigation plan for eteplirsen, (EMA-001722-PIP01-14-M02) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council

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<sup>1</sup>,

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<sup>2</sup>,

Having regard to the European Medicines Agency's decision P/0029/2016 issued on 29 January 2016 and the decision P/0279/2016 issued on 7 October 2016,

Having regard to the application submitted by Sarepta Therapeutics Ireland Limited on 20 March 2019 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and proposing a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 28 June 2019, in accordance with Article 22 of Regulation (EC) No 1901/2006 and Article 13 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 acceptance of changes to the agreed paediatric investigation plan and on the granting of a waiver.
- (2) It is therefore appropriate to adopt a decision on the acceptance of changes to the agreed paediatric investigation plan.
- (3) It is therefore appropriate to adopt a decision granting a waiver.

---

<sup>1</sup> OJ L 378, 27.12.2006, p.1.

<sup>2</sup> 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, intravenous 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**

A waiver for eteplirsen, concentrate for solution for infusion, intravenous use, the details of which are set out in the opinion of the Paediatric Committee the European Medicines Agency annexed hereto, together with its appendices, is hereby granted.

**Article 3**

This decision is addressed to Sarepta Therapeutics Ireland Limited, Regus House, Harcourt Centre, Harcourt Road, D02 HW77 – Dublin 2, Ireland.



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

EMA/PDCO/232337/2019 Corr  
Amsterdam, 28 June 2019

## Opinion of the Paediatric Committee on the acceptance of a modification of an agreed Paediatric Investigation Plan EMA-001722-PIP01-14-M02

### Scope of the application

#### Active substance(s):

Eteplirsén

#### Condition(s):

Treatment of Duchenne muscular dystrophy

#### Pharmaceutical form(s):

Concentrate for solution for infusion

#### Route(s) of administration:

Intravenous use

#### Name/corporate name of the PIP applicant:

Sarepta Therapeutics Ireland Limited

### Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Sarepta Therapeutics Ireland Limited submitted to the European Medicines Agency on 20 March 2019 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, and the decision P/0279/2016 issued on 7 October 2016.

The application for modification proposed changes to the agreed paediatric investigation plan and proposed a waiver

The procedure started on 30 April 2019.



## Scope of the modification

Some measures and timelines of the Paediatric Investigation Plan have been modified. A waiver for a new paediatric subset has been added.

## 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;
  - to grant a waiver for one or more subsets of the paediatric population concluded in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

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 and the subset(s) of the paediatric population and condition(s) covered by the waiver 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

## 1.1. Condition:

Treatment of Duchenne muscular dystrophy

The waiver applies to:

- the paediatric population from birth to less than 6 months of age;
- concentrate for solution for infusion, intravenous use;
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.

# 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 6 months of age to less than 18 years of age

### 2.1.3. Pharmaceutical form(s)

Concentrate for solution for infusion

### 2.1.4. Measures

| Area                    | Number of measures | Description  |
|-------------------------|--------------------|--|
| Quality-related studies | 1                  | <b>Study 1</b><br>Development of an age-appropriate concentrate for solution for infusion for intravenous use.<br><b>Study 2</b><br>Study deleted in procedure EMEA-001722-PIP01-14-M02.                           |
| Non-clinical studies    | 2                  | <b>Study 3</b><br>Definitive juvenile toxicity study to evaluate the toxicity and toxicokinetics of eteplirsén in male juvenile rats in a 10-week repeat-dose study with a 4-week recovery period. (4658-tox-003). |

|                  |   |  |
|------------------|---|--|
|                  |   | <p><b>Study 4</b></p> <p>Pharmacokinetic study of eteplirsen in male rats following administration of a single subcutaneous or intravenous dose.</p> <p><b>Study 5</b></p> <p>Study deleted in procedure EMEA-001722-PIP01-14-M02.</p>   |
| Clinical studies | 8 | <p><b>Study 6</b></p> <p>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)</p> <p><b>Study 7</b></p> <p>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 )</p> <p><b>Study 8</b></p> <p>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)</p> <p><b>Study 9</b></p> <p>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)</p> <p><b>Study 10</b></p> <p>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)</p> <p><b>Study 11</b></p> <p>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)</p> |

|   |   |  |
|---|---|--|
|   |   | <p><b>Study 12</b></p> <p>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)</p> <p><b>Study 13</b></p> <p>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)</p> <p><b>Study 14</b></p> <p>Study deleted in procedure EMEA-001722-PIP01-14-M02.</p> <p><b>Study 15</b></p> <p>Study deleted in procedure EMEA-001722-PIP01-14-M02.</p> <p><b>Study 16</b></p> <p>Study deleted in procedure EMEA-001722-PIP01-14-M02.</p> |
| Extrapolation, modelling and simulation studies | 2 | <p><b>Study 17</b></p> <p>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.</p> <p><b>Study 18</b></p> <p>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.</p> <p><b>Study 19</b></p> <p>Study deleted in procedure EMEA-001722-PIP01-14-M02.</p>   |
| 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           |