EMA/413460/2020

European Medicines Agency decision

P/0302/2020

of 12 August 2020

on the acceptance of a modification of an agreed paediatric investigation plan for synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues (fitusiran) (EMEA-001855-PIP01-15-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.

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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/0186/2019 issued on 15 May 2019 and the decision P/0424/2019 issued on 4 December 2019,

Having regard to the application submitted by Genzyme Europe B.V. on 24 March 2020 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral and a waiver,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 26 June 2020, 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 for synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues (fitusiran), solution for injection, 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 Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP – Amsterdam, The Netherlands.

EMA/PDCO/195835/2020
Amsterdam, 26 June 2020

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

EMEA-001855-PIP01-15-M02

Scope of the application

Active substance(s):

Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues (fitusiran)

Condition(s):

Treatment of congenital haemophilia A

Treatment of congenital haemophilia B

Pharmaceutical form(s):

Solution for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

Genzyme Europe B.V.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Genzyme Europe B.V. submitted to the European Medicines Agency on 24 March 2020 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/0186/2019 issued on 15 May 2019 and the decision P/0424/2019 issued on 4 December 2019.

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

The procedure started on 30 April 2020.

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 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 congenital haemophilia A

The waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- solution for injection, subcutaneous use;
- on the grounds that the specific medicinal product is likely to be unsafe.

1.2. Condition

Treatment of congenital haemophilia B

The waiver applies to:

- the paediatric population from birth to less than 1 year of age;
- solution for injection, subcutaneous use;
- on the grounds that the specific medicinal product is likely to be unsafe.

2. Paediatric investigation plan

2.1. Condition

Treatment of congenital haemophilia A

2.1.1. Indication(s) targeted by the PIP

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children aged $\geqslant$ 1 year with severe congenital haemophilia A, including patients who express neutralizing antibodies to exogenous factor VIII substitution.

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

From 1 to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Solution for injection

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	0	Not applicable
Non-clinical studies	1	**Study 1** Dose range-finding juvenile toxicity study to evaluate the potential toxicity of fitusiran in neonate Sprague-Dawley rats (9000727)
Clinical studies	7	**Study 2** Randomized, open-label, parallel group study comparing fitusiran to on-demand bypassing agents (BPA) in patients from 12 to less than 18 years of age (and adults) with haemophilia A or B who express inhibitors to replacement factor therapy and who receive on demand treatment for bleeding episodes. The objectives are to evaluate efficacy, safety, PK, PD and HRQoL (ALN-AT3SC-003; Sanofi Genzyme EFC14768) **Study 3** Randomized, open-label, parallel group study comparing fitusiran to on-demand bypassing agents (BPA) in patients from 12 to less than 18 years of age (and adults) with haemophilia A or B without inhibitors to replacement factor therapy and who receive on demand treatment for bleeding episodes. The objectives are to evaluate efficacy, safety, PK, PD and HRQoL (ALN-AT3SC-004; Sanofi Genzyme EFC14769). **Study 4** Open-label, single-arm, one-way crossover study initiated for haemophilia A and B patients from 12 to less than 18 years of age (and adults) with and without inhibitors, previously treated with prophylactic Factor VIII or Factor IX or bypassing agents (BPAs). Intra patient comparison of patients treated with fitusiran to previous standard of care prophylaxis treatment (run-in period). The objective of the study is to assess the efficacy and safety of fitusiran administration as prophylaxis (ALN-AT3SC-009; Sanofi Genzyme EFC15110)

		Study 5 Open-label extension study with patients from studies ALN-AT3SC-003, ALN-AT3SC-004 and ALN-AT3SC-009. The main objective of the study is to assess the efficacy and safety of long-term administration of fitusiran (LTE15174) **Study 6** Open-label, non-comparative study in patients from 1 to less than 12 years of age with severe haemophilia A or B who express inhibitors to replacement factor therapy and who receive on demand treatment for bleeding episodes. The objectives are to evaluate safety, PK and PD (ATLAS Paediatrics Study Part A, EFC15467). **Study 7** Non-interventional study to characterise bleeding episodes on standard of care in patients from 1 to less than 12 years of age with severe haemophilia A and B, with and without inhibitors, receiving prophylactic factor VIII/IX or bypassing agent treatment. The objective of this study is to generate data for an intra patient comparison for PIP Study 8/ATLAS Paediatrics Study Part B/EFC15467, (ATLAS Non - Interventional Paediatric Study). **Study 8** Open label, single arm study in patients from 1 to less than 12 years of age with severe haemophilia A or B, with and without inhibitors, previously receiving prophylactic factor VIII/IX or bypassing agent treatment. Intra patient comparison to previous standard of care prophylaxis treatment (patients from PIP Study 7/Non-interventional study). The objectives are to evaluate efficacy and safety of fitusiran administration as prophylaxis (ATLAS Paediatrics Study Part B, EFC15467)
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable
Other measures	0	Not applicable

2.2. Condition

Treatment of congenital haemophilia B

2.2.1. Indication(s) targeted by the PIP

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in children aged ⩾ 1 year with severe congenital haemophilia B, including patients who express neutralizing antibodies to exogenous factor IX substitution

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

From 1 to less than 18 years of age

2.2.3. Pharmaceutical form(s)

Solution for injection

2.2.4. Measures

Area	**Number of measures**	**Description**
Quality-related studies	0	Not applicable
Non-clinical studies	1	**Study 1** Same as Study 1 for *Treatment of congenital Haemophilia A*
Clinical studies	7	**Study 2** Same as Study 2 for *Treatment of congenital Haemophilia A* **Study 3** Same as Study 3 for *Treatment of congenital Haemophilia A* **Study 4** Same as Study 4 for *Treatment of congenital Haemophilia A* **Study 5** Same as Study 5 for *Treatment of congenital Haemophilia A* **Study 6** Same as Study 6 for *Treatment of congenital Haemophilia A*

		Study 7 Same as Study 7 for *Treatment of congenital Haemophilia A* **Study 8** Same as Study 8 for *Treatment of congenital Haemophilia A*
Extrapolation, modelling and simulation studies	0	Not applicable
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 July 2025
Deferral for one or more measures contained in the paediatric investigation plan:	Yes