EMA/256057/2019

European Medicines Agency decision

P/0186/2019

of 15 May 2019

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver 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) 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 application submitted by Alnylam UK Limited on 23 November 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 29 March 2019, in accordance with Article 17 of Regulation (EC) No 1901/2006 and Article 21 of said Regulation 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 agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver.

(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.

(4) It is therefore appropriate to adopt a decision granting a waiver.

[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 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, 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 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, 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

A waiver 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, 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 4

This decision is addressed to Genzyme Europe B.V., Paasheuvelweg 25, 1105 BP - Amsterdam, The Netherlands.

EMA/PDCO/4916/2019 Corr
Amsterdam, 29 March 2019

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

EMEA-001855-PIP01-15

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 16(1) of Regulation (EC) No 1901/2006 as amended, Alnylam UK Limited submitted for agreement to the European Medicines Agency on 23 November 2015 an application for a paediatric investigation plan and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation for the above mentioned medicinal product.

The procedure started on 4 January 2016.

On 20 February 2018 the ownership of fitusiran has been transferred from Alnylam UK Limited to Genzyme Europe B.V.

Supplementary information was provided by the applicant on 20 December 2018. The applicant proposed modifications to the paediatric investigation plan.

A meeting with the Paediatric Committee took place on 28 March 2019.

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 17(1) of said Regulation;
   - to grant a deferral in accordance with Article 21 of said Regulation;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population.

   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

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 ⩾ 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