MHRA
10 South Colonnade
Canary Wharf
London
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United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

accept change(s) to the agreed paediatric investigation plan and to the deferral.

MHRA-101283-PIP01-23-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

Condition(s)

Treatment of Haemophilia A, Treatment of Haemophilia B

Pharmaceutical Form(s)

Solution for injection

Route(s) of Administration

SUBCUTANEOUS USE

Name / Corporate name of the PIP applicant

Sanofi B.V.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Sanofi B.V. submitted to the licensing authority on 03/10/2024 13:22 BST an application for a Modification

The procedure started on 05/11/2024 08:52 GMT

1. The licensing authority, having assessed the application in accordance with the Human Medicines Regulations 2012, decides, as set out in the appended summary report:

to accept change(s) to the agreed paediatric investigation plan and to the deferral

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

This decision is forwarded to the applicant, together with its annex and appendix.

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Final Decision Letter

MHRA-101283-PIP01-23-M02

Of 28/01/2025 12:38 GMT

On the adopted decision for Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues (MHRA-101283-PIP01-23-M02) in accordance with the Human Medicines Regulations 2012.

The licensing authority, in accordance with the Human Medicines Regulations 2012, has adopted this decision:

Agreement on modification of a paediatric investigation plan (including modification of a waiver or deferral included in that paediatric investigation plan)

This decision applies to a Modification for Synthetic double-stranded siRNA oligonucleotide directed against antithrombin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues, Solution for injection , SUBCUTANEOUS USE .

This decision is addressed to Sanofi B.V., Paasheuvelweg 25, Amsterdam, NETHERLANDS, 1105 BP

ANNEX I

1. Waiver

1.1 Condition:

Condition 1: Treatment of congenital haemophilia A The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 1 year of age. Pharmaceutical form(s): Solution for injection Route(s) of administration: SUBCUTANEOUS USE Reason for granting waiver: On the grounds the specific medicinal product is likely to be unsafe. Condition 2: Treatment of congenital haemophilia B. The waiver applies / applied to: Paediatric Subset(s): The paediatric population from birth to less than 1 year of age. Pharmaceutical form(s): Solution for injection Route(s) of administration: SUBCUTANEOUS USE Reason for granting waiver: On the grounds the specific medicinal product is likely to be unsafe.

2. Paediatric Investigation Plan:

2.1 Condition(s):

Condition 1: Treatment of congenital haemophilia A Condition 2: Treatment of congenital haemophilia B.

2.2 Indication(s) targeted by the PIP:

Condition 1: 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 neutralising antibodies to exogenous factor VIII substitution. Condition 2: 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 neutralising antibodies to exogenous factor IX substitution.

2.3 Subset(s) of the paediatric population concerned by the paediatric development:

Condition 1: The paediatric population from 1 year to less than 18 years of age. Condition 2: The paediatric population from 1 year to less than 18 years of age.

2.4 Pharmaceutical Form(s):

Condition 1: Solution for injection Condition 2: Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	0	Not applicable.
Non-Clinical Studies	1	(Same study for conditions 1 and 2) Study 1 (9000727) Dose range-finding juvenile toxicity study to evaluate the potential toxicity of fitusiran in neonate Sprague-Dawley rats.
Clinical Studies	7	(Same studies for conditions 1 and 2) Study 2 (ALN-AT3SC-003, Sanofi Genzyme EFC14768) Randomised, open-label, parallel group study comparing fitusiran to on-demand bypassing agents (BPA) in patients from 12 years 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. Study 3 (ALN-

		AT3SC-004; Sanofi Genzyme EFC14769) Randomised, open-label, parallel group study comparing fitusiran to on-demand Factor VIII or IX only in patients from 12 years 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. Study 4 (ALN-AT3SC-009; Sanofi Genzyme EFC15110) Open-label, single-arm, one-way crossover study initiated for haemophilia A and B patients from 12 years 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.
Extrapolation, Modeling & Simulation Studies	1	(Same study for conditions 1 and 2) Study 10 (SIM0536) (This study was added during procedure MHRA-101283-PIP01-23-M02) Population Kinetic-Pharmacodynamic (PopK-PD) Analysis to characterise Antithrombin Activity following treatment with fitusiran in Paediatric Participants with Haemophilia.
Other Studies	0	(Same clinical studies for conditions 1 and 2, continued) Study 5 (LTE15174) Open-label extension study to studies ALN-AT3SC-003 (EFC14768), ALN-AT3SC-004 (EFC14769) and ALN-AT3SC-009 (EFC15110). The main objective of the study is to assess the efficacy and safety of long-term administration of fitusiran. Study 6 (ATLAS Paediatrics Study Part A, EFC15467) Open-label, non-comparative study in patients from 1 year 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. Study 7 (ATLAS Non - Interventional Paediatric Study) This study was deleted during procedure MHRA-101283-PIP01-23-M01. Study 8 (ATLAS Paediatrics Study, EFC17905) Open-label, single group, two arm study to evaluate the efficacy and safety of fitusiran prophylaxis in paediatric subjects ages 1 year to less than 12 years with severe haemophilia A or B, with or without inhibitors, previously receiving factor or BPA treatments. Study 9 (EFC17574, ATLAS NEO) (This study was added during procedure MHRA-101283-PIP01-23-M01) Open-label, single-arm, one-way crossover study to evaluate the efficacy and safety of fitusiran prophylaxis in male participants aged from 12 years to less than 18 years of age (and adults) with severe haemophilia A or B, with or without inhibitory antibodies to Factor VIII or IX, who have switched from their prior Clotting Factor Concentrate (CFC) or Bypassing Agents (BPA) standard of care (SOC) treatment.
Other Measures	0	Not applicable.

3. Follow-up, completion and deferral of a PIP:

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	30/06/2030
Deferral of one or more studies contained in the paediatric investigation plan:	Yes