MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

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Decision Cover Letter

Decision of the licensing authority to:

agree a paediatric investigation plan and grant a deferral

MHRA-101827-PIP01-25

Scope of the Application

Active Substance(s)

Apazunersen

Condition(s)

Treatment of Angelman syndrome

Pharmaceutical Form(s)

Solution for injection

Route(s) of Administration

Intrathecal use

Name / Corporate name of the PIP applicant

Ultragenyx Netherlands B.V.

Basis for the Decision

Pursuant to the Human Medicines Regulations 2012, Ultragenyx Netherlands B.V. submitted to the licensing authority on 18/12/2025 14:06 GMT an application for a

The procedure started on 09/01/2026 12:13 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 agree a paediatric investigation plan and grant a 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-101827-PIP01-25

Of 04/08/2026 07:36 BST

On the adopted decision for 2′-O, 4′-C-methylene-P-thio-adenylyl-(3′→5′)-2′-O, 4′-C-methylene-P-thio-guanylyl-(3′ →5′)-2′-O, 4′-C-methylene-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′→5′)-2′-deoxy-P-thio-guanylyl-(3′→5′)-2′-deoxy-P-thio-guanylyl-(3′→5′)-2′-deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′- deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′→5′)- 2′-deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′ →5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-cytidylyl-(3′→5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-uridylyl-(3′→5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-uridylyl-(3′→5′)-2′-O, 4′-C-methyleneguanosine, heptadecasodium salt; Apazunersen (MHRA-101827-PIP01-25) 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 a paediatric investigation plan

This decision applies to a for 2′-O, 4′-C-methylene-P-thio-adenylyl-(3′→5′)-2′-O, 4′-C-methylene-P-thio-guanylyl-(3′ →5′)-2′-O, 4′-C-methylene-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′→5′)-2′-deoxy-P-thio-guanylyl-(3′→5′)-2′-deoxy-P-thio-guanylyl-(3′→5′)-2′-deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′- deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-adenylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′→5′)- 2′-deoxy-P-thio-cytidylyl-(3′→5′)-2′-deoxy-P-thio-thymidylyl-(3′ →5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-cytidylyl-(3′→5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-uridylyl-(3′→5′)-2′-O, 4′-C-methylene-5-methyl-P-thio-uridylyl-(3′→5′)-2′-O, 4′-C-methyleneguanosine, heptadecasodium salt; Apazunersen , Solution for injection , INTRATHECAL .

This decision is addressed to Ultragenyx Netherlands B.V., Evert van de Beekstraat 1, Schiphol, NETHERLANDS, 1118 CL

ANNEX I

1. Waiver

1.1 Condition:

Not applicable

2. Paediatric Investigation Plan:

2.1 Condition(s):

Treatment of Angelman syndrome

2.2 Indication(s) targeted by the PIP:

Treatment of Angelman syndrome (AS)

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

All subsets of the paediatric population from birth to less than 18 years of age

2.4 Pharmaceutical Form(s):

Solution for injection

2.5 Studies:

Study Type	Number of Studies	Study Description
Quality Measures	0	Not applicable.
Non-Clinical Studies	4	Study 1 (9001356) Juvenile toxicity study in rats to support the evaluation of safety of apazunersen when used in paediatric population. Study 2 (9001522) Juvenile toxicity study in rats to support the evaluation of safety of apazunersen when used in paediatric population. Study 3 (5500299) Juvenile toxicity study in cynomolgus monkeys to support the evaluation of safety of apazunersen in the paediatric population. Study 4 (5500401) Juvenile toxicity study in cynomolgus monkeys to support the evaluation of safety of apazunersen in the paediatric population.
Clinical Studies	3	Study 5 (GTX-102-001) Open-label, multiple-dose, dose-escalating trial to evaluate the safety, tolerability and pharmacokinetics of apazunersen in participants from 4 years to less

		than 18 years of age with Angelman syndrome. Study 6 (GTX-102-CL301) Double-blind, randomised, sham-controlled trial to evaluate safety and efficacy of apazunersen in ambulatory participants from 4 years to less than 18 years of age with deletion-type Angelman syndrome. Study 7 (GTX-102-CL210) Open-label, baseline-controlled basket trial to evaluate pharmacokinetics, safety, and efficacy of apazunersen in participants from 1 year to less than 18 years of age with deletion- or non-deletion-type Angelman syndrome.
Extrapolation, Modeling & Simulation Studies	1	Extrapolation Plan Study 6 (GTX-102-CL301) and Study 7 (GTX-102-CL210) are part of an extrapolation approach with the objective to support the extrapolation of efficacy data from the source to the target populations using a Bayesian Hierarchical Model (BHM).
Other Studies	0	Not applicable.
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:	No
Date of completion of the paediatric investigation plan:	31/12/2030
Deferral of one or more studies contained in the paediatric investigation plan:	Yes