EMA/155211/2011

European Medicines Agency decision

P/54/2011

of 4 March 2011

on the agreement of a paediatric investigation plan and on the granting of a deferral for 2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridine sodium salt, also known as exon 51 specific phosphorothioate oligonucleotide (EMEA-000746-PIP01-09) 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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European Medicines Agency decision

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on the agreement of a paediatric investigation plan and on the granting of a deferral for 2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridine sodium salt, also known as exon 51 specific phosphorothioate oligonucleotide (EMEA-000746-PIP01-09) 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[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 Glaxo Group Limited on 31 March 2010 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 14 January 2011, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 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.

(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.

[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 2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3' →5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3' →5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→ 5' O,O-phosphorothioyl)-2'-O-methyl-uridine sodium salt, also known as exon 51 specific phosphorothioate oligonucleotide, 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 2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3' → 5' O,O-phosphorothioyl)-2'-O-methyl-uridine sodium salt, also known as exon 51 specific phosphorothioate oligonucleotide, 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

This decision is addressed to Glaxo Group Limited, Glaxo Wellcome House, Berkeley Avenue, UB6 0NN Greenford, United Kingdom.

Done at London, 4 March 2011

For the European Medicines Agency
Andreas Pott
Acting Executive Director

(Signature on file)

EMA/PDCO/779587/2010

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

EMEA-000746-PIP01-09

Scope of the application

Active substance(s):

2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-guanosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-adenosylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-cytidylyl-(3'→5' O,O-phosphorothioyl)-2'-O-methyl-uridine sodium salt

Also known as exon 51 specific phosphorothioate oligonucleotide

Condition(s):

Treatment of patients with Duchenne muscular dystrophy

Pharmaceutical form(s):

Solution for injection

Route(s) of administration:

Subcutaneous use

Name/corporate name of the PIP applicant:

Glaxo Group Limited

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Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Glaxo Group Limited submitted for agreement to the European Medicines Agency on 31 March 2010 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation.

The procedure started on 20 May 2010.

Supplementary information was provided by the applicant on 3 November 2010 and 17 December 2010.

A meeting with the Paediatric Committee took place on 14 January 2011.

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 18 of said Regulation,
   - to grant a deferral in accordance with Article 21 of said Regulation,

   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(es) and appendix.

London, 14 January 2011

On behalf of the Paediatric Committee
Dr Daniel Brasseur, Chairman

(Signature on file)

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

1. Waiver

Not applicable.

2. Paediatric Investigation Plan

2.1. Condition: Treatment of patients with Duchenne muscular dystrophy

2.1.1. Indication(s) targeted by the PIP

Treatment of patients with Duchenne muscular dystrophy bearing mutations that can be corrected by skipping exon 51.

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

From birth to less than 18 years of age.

2.1.3. Pharmaceutical form(s)

Solution for injection

2.1.4. Studies

Area	Number of studies	Description
Quality	2	1. Development of the same formulation in a lower strength suitable for the low doses that need to be administered to children below 6 months of age to ensure accuracy of the administered dose. 2. Feasibility of the development of a pre-filled syringe product.
Non-clinical	1	3. 8-week subcutaneous general juvenile mouse toxicity study including plasma toxicokinetics, developmental immunotoxicity and recovery of any toxicity after 4 weeks off-dose of exon 51 specific phosphorothioate oligonucleotide.
Clinical	7	4. Double blind, parallel-group, placebo-controlled, exploratory clinical study to assess long-term safety, tolerability, efficacy and pharmacokinetics of exon 51 specific phosphorothioate oligonucleotide in non-ambulant patients above 9 years of age with Duchenne muscular dystrophy with the potential for an initial natural history observation period. 5. Double-blind, escalating dose, randomised, placebo-controlled study to assess the pharmacokinetics, safety and tolerability of exon 51 specific phosphorothioate oligonucleotide in non-ambulant patients above 9 years of age with Duchenne muscular dystrophy 6. Double blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of exon 51 specific phosphorothioate oligonucleotide for efficacy, safety, tolerability and pharmacokinetics in ambulant patients 5 years and above with Duchenne muscular dystrophy 7. Randomised, double blind, placebo-controlled clinical study to assess the efficacy and safety of exon 51 specific phosphorothioate oligonucleotide in

Area	Number of studies	Description
		ambulant patients 5 years and above with Duchenne muscular dystrophy. 8. A long-term, open-label safety study of exon 51 specific phosphorothioate oligonucleotide in ambulant patients 5 years and above with Duchenne muscular dystrophy for participants in feeder studies e.g. DMD114117 or DMD114044 9. Open label, escalating dose ranging study to assess the safety, tolerability, pharmacokinetics and efficacy, of multiple subcutaneous doses of exon 51 specific phosphorothioate oligonucleotide in patients with Duchenne muscular dystrophy from birth to below 5 years of age in the presence and absence of corticosteroid therapy. 10. Randomised, double blind, parallel-group, placebo-controlled confirmatory study to assess the efficacy and safety of exon 51 specific phosphorothioate oligonucleotide in non-ambulatory patients with Duchenne muscular dystrophy.

3. Follow-up, completion and deferral of PIP

Measures to address long term follow-up of potential safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By Dec 2016
Deferral for one or more studies contained in the paediatric investigation plan:	Yes