EMA/764016/2011

European Medicines Agency decision

P/255/2011

of 26 October 2011

on the acceptance of a modification of an agreed 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 (exon 51 specific phosphorothioate oligonucleotide) (EMEA-000746-PIP01-09-M01) 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.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8409
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

European Medicines Agency decision

P/255/2011

of 26 October 2011

on the acceptance of a modification of an agreed 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 (exon 51 specific phosphorothioate oligonucleotide) (EMEA-000746-PIP01-09-M01) 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 European Medicines Agency's decision P/54/2011 issued on 4 March 2011,

Having regard to the application submitted by Glaxo Group Limited on 1 July 2011 under Article 22 of Regulation (EC) No 1901/2006 proposing changes to the agreed paediatric investigation plan with a deferral,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 9 September 2011, in accordance with Article 22 of Regulation (EC) No 1901/2006,

Having regard to Article 25 of Regulation (EC) No 1901/2006,

[1] OJ L 378, 27.12.2006, p.1.
[2] OJ L 136, 30.4.2004, p. 1.

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.

Has adopted this decision:

Article 1

Changes to the agreed 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 (exon 51 specific phosphorothioate oligonucleotide), 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 Glaxo Group Limited, Glaxo Wellcome House, Berkeley Avenue, Greenford, UB6 0NN – London, United Kingdom.

Done at London, 26 October 2011

For the European Medicines Agency
Andreas Pott
Acting Executive Director
(Signature on file)

EMA/PDCO/522998/2011

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

EMEA-000746-PIP01-09-M01

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

(exon 51 specific phosphorothioate oligonucleotide)

Condition(s):

Treatment of 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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Glaxo Group Limited submitted to the European Medicines Agency on 1 July 2011 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/54/2011 issued on 4 March 2011.

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

The procedure started on 13 July 2011.

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 Icelandic and the Norwegian Paediatric Committee members agree with the above-mentioned recommendation of the Paediatric Committee.

2. The measures and timelines of the 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.

London, 9 September 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, escalating dose, randomised, placebo-controlled study to assess the pharmacokinetics, safety and tolerability of exon 51 specific phosphorothioate oligonucleotide in non-ambulant patients aged 9 years and above with Duchenne muscular dystrophy (DMD114118). 5. 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 (DMD114117). 6. Randomised, double blind, placebo-controlled clinical study to assess the efficacy and safety of exon 51 specific phosphorothioate oligonucleotide in ambulant patients 5 years and above with Duchenne muscular dystrophy (DMD114044). 7. Double blind, parallel-group, placebo-controlled, exploratory clinical study to assess long-term safety, tolerability, efficacy and pharmacokinetics of

Area	Number of studies	Description
		exon 51 specific phosphorothioate oligonucleotide in non-ambulant patients aged 9 years and above with Duchenne muscular dystrophy with an initial placebo-controlled dose escalation period (DMD114348). 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 (DMD114349). 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 (DMD114402). 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 (identifier not yet assigned).

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety and efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2017
Deferral for one or more studies contained in the paediatric investigation plan:	Yes