EMA/719228/2014

European Medicines Agency decision

P/0337/2014

of 22 December 2014

on the acceptance of a modification of an agreed paediatric investigation plan for lumacaftor / ivacaftor (EMEA-001582-PIP01-13-M02) 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 7523 70405555
Contact EMA www.ema.europa.eu/contact

European Medicines Agency decision

P/0337/2014

of 22 December 2014

on the acceptance of a modification of an agreed paediatric investigation plan for lumacaftor / ivacaftor (EMEA-001582-PIP01-13-M02) 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/0118/2014 issued on 6 May 2014,

Having regard to the application submitted by Vertex Pharmaceuticals (Europe) Ltd. on 26 August 2014 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 14 November 2014, in accordance with Article 22 of Regulation (EC) No 1901/2006,

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 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.

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

Has adopted this decision:

Article 1

Changes to the agreed paediatric investigation plan for lumacaftor / ivacaftor, film-coated tablet, age appropriate oral solid formulation, oral 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 Vertex Pharmaceuticals (Europe) Ltd., 86-88 Jubilee Avenue, Milton Park, OX14 4RW – Abingdon, United Kingdom.

Done at London, 22 December 2014

For the European Medicines Agency
Zaide Frias
Head of Division (ad interim)
Human Medicines Research and Development Support
(Signature on file)

EMA/PDCO/529187/2014

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

EMEA-001582-PIP01-13-M02

Scope of the application

Active substance(s):

Lumacaftor / ivacaftor

Condition(s):

Treatment of cystic fibrosis

Pharmaceutical form(s):

Film-coated tablet

Age appropriate oral solid formulation

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

Vertex Pharmaceuticals (Europe) Ltd.

Basis for opinion

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Vertex Pharmaceuticals (Europe) Ltd. submitted to the European Medicines Agency on 26 August 2014 an application for modification of the agreed paediatric investigation plan with a deferral as set out in the European Medicines Agency's decision P/0118/2014 issued on 6 May 2014.

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

The procedure started on 16 September 2014.

A meeting with the Paediatric Committee took place on 12 November 2014.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5510
Send a question via our website www.ema.europa.eu/contact

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, 14 November 2014

On behalf of the Paediatric Committee
Dr Dirk Mentzer, 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 (PIP)

1. Waiver

Not applicable

2. Paediatric Investigation Plan

2.1. Condition: treatment of cystic fibrosis

2.1.1. Indication(s) targeted by the PIP

Treatment of cystic fibrosis

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)

Film-coated tablet

Age appropriate oral solid formulation

2.1.4. Measures

Area	Number of studies	Description
Quality-related studies	2	1. Development of an age-appropriate fixed-dose combination film-coated tablet for children aged 6 to less than 12 years old. 2. Development of an age appropriate oral solid formulation for children below 6 years of age.
Non-clinical studies	7	3. 6-month oral (gavage) toxicity and toxicokinetics study with lumacaftor and VRT-0995096 in rats with a 1-month recovery (VX-809-TX-012). 4. 3-month oral (gavage) toxicity and toxicokinetics study with lumacaftor, ivacaftor, and VRT-0995096 in rats with a 1-month recovery (VX-809-TX-013). 5. 12 month oral (gavage) toxicity and toxicokinetics study with lumacaftor in Beagle dogs with a 1-month recovery (VX-809-TX-014). 6. Developmental and Perinatal/Postnatal Reproduction Toxicity Study in Rats, Including a Postnatal Behavioral/Functional Evaluation (VX-809-TX-017). 7. Fertility and early embryonic development study in rats with lumacaftor and VRT-0995096 (VX-809-TX-016). 8. Oral (gavage) dose range finding study in juvenile rats (VX-809-TX).

Area	Number of studies	Description
		9. Oral (gavage) toxicity and toxicokinetics study in juvenile rats with 4-week recovery (VX-809-TX).
Clinical studies	8	10. Open-label, multi-dose study to evaluate the pharmacokinetics (PK) and safety of lumacaftor in combination with ivacaftor and their respective major circulating metabolites in subjects with Cystic Fibrosis (CF) who are homozygous for the F508del-CFTR mutation aged 6 to less than 12 years. (StudyVX13-809-011 Part A). 11. Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety and PK in subjects with CF homozygous for the F508del-CFTR mutation aged 6 to less than 12 years. (Study11). 12. Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety in subjects with CF who are homozygous for the F508del-CFTR mutation aged 12 to less than 18 years (and adults). (Study VX12-809-103). 13. Randomised, double-blind, placebo-controlled study to evaluate efficacy and safety in subjects with CF who are homozygous for the F508del-CFTR mutation aged 12 to less than 18 years (and adults). (Study VX12-809-104). 14. Rollover open-label long-term safety and efficacy study in subjects with CF who are homozygous for the F508del-CFTR mutation aged 6 to less than 18 years (and adults) (StudyVX12-809-105). 15. Pharmacokinetic and safety study in subjects with CF who are homozygous for the F508del-CFTR mutation aged 2 to less than 6 years (Study 15). 16. Pharmacokinetic and safety study in subjects with CF who are homozygous for the F508del-CFTR mutation from birth to less than 2 years of age (Study 16). 17. Relative bioavailability study to characterize the PK of the paediatric age appropriate formulation relative to the tablet formulation in healthy adults.
Extrapolation, modelling & simulation studies		Not applicable.
Other studies		Not applicable.
Other measures		Not applicable.

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 July 2017
Deferral for one or more studies contained in the paediatric investigation plan:	Yes