EMA/587832/2014

European Medicines Agency decision

P/0286/2014

of 28 October 2014

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for cholera vaccine, live attenuated, oral (strain CVD 103-HgR) (EMEA-001490-PIP01-13) 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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on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for cholera vaccine, live attenuated, oral (strain CVD 103-HgR) (EMEA-001490-PIP01-13) 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 PaxVax Inc. on 7 June 2013 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 12 September 2014, in accordance with Article 18 of Regulation (EC) No 1901/2006, and Article 21 of said Regulation and Article 13 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 and on the granting of a waiver.

(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.

(4) It is therefore appropriate to adopt a decision granting a waiver.

[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 cholera vaccine, live attenuated, oral (strain CVD 103-HgR), powder for oral suspension, age-appropriate oral liquid dosage form, oral 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 cholera vaccine, live attenuated, oral (strain CVD 103-HgR), powder for oral suspension, age-appropriate oral liquid dosage form, oral 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

A waiver for cholera vaccine, live attenuated, oral (strain CVD 103-HgR), powder for oral suspension, age-appropriate oral liquid dosage form, oral 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 4

This decision is addressed to PaxVax Inc., 3985-A Sorrento Valley Blvd., CA 92121 – San Diego, United States.

Done at London, 28 October 2014

For the European Medicines Agency
Guido Rasi
Executive Director
(Signature on file)

EMA/PDCO/392485/2014

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

EMEA-001490-PIP01-13

Scope of the application

Active substance(s):

Cholera vaccine, live attenuated, oral (strain CVD 103-HgR)

Condition(s):

Prevention of cholera

Pharmaceutical form(s):

Powder for oral suspension

Age-appropriate oral liquid dosage form

Route(s) of administration:

Oral use

Name/corporate name of the PIP applicant:

PaxVax Inc.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, PaxVax Inc. submitted for agreement to the European Medicines Agency on 7 June 2013 an application for a paediatric investigation plan for the above mentioned medicinal product and a waiver under Article 13 of said Regulation.

The procedure started on 17 July 2013.

Supplementary information was provided by the applicant on 20 June 2014. The applicant proposed modifications to the paediatric investigation plan and requested a deferral.

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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;
   - to grant a waiver for one or more subsets of the paediatric population in accordance with Article 13 of said Regulation and concluded in accordance with Article 11(1)(a) of said Regulation, on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population.

   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 agreed paediatric investigation plan and the subset(s) of the paediatric population and condition(s) covered by the waiver 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, 12 September 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

1.1. Condition:

Prevention of cholera

The waiver applies to:

- the paediatric population from birth to less than 6 months of age;
- powder for oral suspension for oral use;
- on the grounds that the specific medicinal product is likely to be ineffective.

2. Paediatric investigation plan

2.1. Condition:

Prevention of cholera

2.1.1. Indication(s) targeted by the PIP

Prophylaxis of disease caused by V. cholerae serogroup O1

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

From 6 months to less than 18 years of age.

2.1.3. Pharmaceutical form(s)

Powder for oral suspension

Age-appropriate oral liquid dosage form

2.1.4. Measures

Area	Number of measures	Description
Quality-related studies	1	**Study 1** Development of an age-appropriate oral liquid dosage form for the paediatric subset from 6 months to less than 2 years of age.
Non-clinical studies	0	Not applicable.

Area	Number of measures	Description
Clinical studies	2	**Study 2** Double-blind, randomised, single dose, placebo-controlled trial to demonstrate that vibriocidal antibody seroconversion in children from 2 to less than 18 years of age is non-inferior as compared to adults following vaccination with cholera vaccine (strain CVD 103-HgR). **Study 3** Double-blind, randomised, single dose, placebo-controlled trial to demonstrate that vibriocidal antibody seroconversion in children from 6 months to less than 2 years of age is non-inferior as compared to adults following vaccination with cholera vaccine (strain CVD 103-HgR).
Extrapolation, modelling and simulation studies	0	Not applicable
Other studies	0	Not applicable
Other measures	0	Not applicable

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	No
Date of completion of the paediatric investigation plan:	By March 2017
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

4. Details of the agreed measures

4.1. Measures to be performed according to the specified timelines

Condition:

Prevention of cholera

4.1.1. Quality-related studies

Study 1

Study identifier(s)	Study 1
Pharmaceutical form required to be developed for paediatric use	Age-appropriate oral liquid dosage form
Study description and objectives for pharmaceutical development	Development of an age-appropriate oral liquid dosage form for the paediatric subset from 6 months to less than 2 years of age not exceeding 50 ml in volume.
Date of completion	By March 2017 The completion of this study is deferred.

4.1.2. Non-clinical studies

Not applicable

4.1.3. Clinical studies

Study 2

Study identifier(s)	PXVX-VC-200-006
Study design features and main objectives	Double-blind, randomised, single dose, placebo-controlled trial to demonstrate that vibriocidal antibody seroconversion in children from 2 to less than 18 years of age is non-inferior as compared to adults following vaccination with cholera vaccine (strain CVD 103-HgR).
Study population and subset definition	Healthy male and female children and adolescents from 2 to less than 18 years of age
Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	At least 330 subjects evaluable for the primary analysis, in the following cohorts: • Cohort 1: at least 110 children from 12 to less than 18 years of age with randomisation ratio 1:1 • Cohort 2: at least 110 children from 6 to less than 12 years of age with randomisation ratio 8:1:1 (active : placebo : placebo) • Cohort 3: at least 110 children from 2 to less than 6 years of age with randomisation ratio 8:1:1 (active : placebo : placebo)
Study duration for participants	• Treatment duration: must be planned for 15 days in protocol • Follow-up duration (part of completion of this study): must be planned for 180 days in protocol
Dosage, treatment	• Cohort 1: 1,000,000,000 CFU of lyophilised cholera vaccine (strain

regimen, route of administration	CVD 103-HgR) administered orally either on Day 1 or Day 15 • Cohort 2: 1,000,000,000 CFU of lyophilised cholera vaccine (strain CVD 103-HgR) administered orally either on Day 1 and Day 15, or on Day 1, or on Day 15 • Cohort 3: 1,000,000,000 CFU of lyophilised cholera vaccine (strain CVD 103-HgR) administered orally either on Day 1 and Day 15, or on Day 1, or on Day 15
Control(s)	Placebo either on Day 1 or on Day 15 Historical control (2500 healthy adults from trial PXVX-VC-200-004)
Primary endpoint(s) with time point(s) of assessment	Proportion of patients with vibriocidal antibody seroconversion within 28 days of vaccination as compared historical control. Time points of assessment: Day 10 and Day 28 following vaccination. Seroconversion defined as a 4-fold increase in vibriocidal antibody titre compared to baseline.
Main secondary endpoint(s) with time(s) of assessment	• Proportion of patients with vibriocidal antibody seroconversion within 14 days of vaccination as compared historical control • Safety assessments • Acceptability and palatability assessments
Statistical plan including study conduct and analysis	• Primary analysis of primary endpoint: non-inferiority of active treatment compared to historical control • Seroconversion will be considered non-inferior if the lower bound on the 95% confidence interval on the difference between the rate in children and in adults does not exceed -20 %.
Other	Not applicable
Plan for specific follow-up	Not determined by the PDCO
External Data Safety Monitoring Board	Required
Date of initiation	Not determined by the PDCO The initiation of this study is deferred.
Date of completion (last patient, last visit)	By September 2015 The completion of this study is deferred.

Study 3

Study identifier(s)	PXVX-VC-200-008
Study design features and main objectives	Double-blind, randomised, single dose, placebo-controlled trial to demonstrate that vibriocidal antibody seroconversion in children from 6 months to less than 2 years of age is non-inferior as compared to adults following vaccination with cholera vaccine (strain CVD 103-HgR).
Study population and subset definition	Healthy male and female children from 6 months to less than 2 years of age

Number of study participants by paediatric subset (e.g. age, sex, severity or stage)	At least 110 subjects evaluable for the primary analysis with randomisation ratio 8:1:1 (active : placebo : placebo)
Study duration for participants	• Treatment duration: must be planned for 15 days in protocol • Follow-up duration (part of completion of this study): must be planned for 180 days in protocol
Dosage, treatment regimen, route of administration	Using pharmaceutical form developed in Study 1 orally administered 1,000,000,000 CFU of lyophilised cholera vaccine (strain CVD 103-HgR) either on Day 1 and Day 15, or on Day 1, or on Day 15
Control(s)	Placebo either on Day 1 or on Day 15 Historical control (2500 healthy adults from trial PXVX-VC-200-004)
Primary endpoint(s) with time point(s) of assessment	Proportion of patients with vibriocidal antibody seroconversion within 28 days of vaccination as compared historical control. Time points of assessment: Day 10 and Day 28 following vaccination. Seroconversion defined as a 4-fold increase in vibriocidal antibody titre compared to baseline.
Main secondary endpoint(s) with time(s) of assessment	• Proportion of patients with vibriocidal antibody seroconversion within 14 days of vaccination as compared historical control • Safety assessments • Acceptability and palatability assessments
Statistical plan including study conduct and analysis	• Primary analysis of primary endpoint: non-inferiority of active treatment compared to historical control • Seroconversion will be considered non-inferior if the lower bound on the 95% confidence interval on the difference between the rate in children and in adults does not exceed -20 %.
Other	Not applicable
Plan for specific follow-up	Not determined by the PDCO
External Data Safety Monitoring Board	Required
Date of initiation	Not determined by the PDCO The initiation of this study is deferred.
Date of completion (last patient, last visit)	By March 2017 The completion of this study is deferred.

4.1.4. Extrapolation, modelling and simulation studies

Not applicable.

4.1.5. Other studies

Not applicable.

4.1.6. Other measures

Not applicable.

5. Potential long-term safety / efficacy issues in relation to paediatric use for consideration in the Risk Management Plan / Pharmacovigilance activities

Based on the data submitted, no long term safety/efficacy issues were considered as particular causes of concern by the PDCO.

6. Reminder

Interventional clinical trials have to be registered with the EudraCT database.

All investigational medicinal products used in the studies or trials must be registered in the EudraVigilance Medicinal Product Dictionary by the sponsor.

Studies or trials which are inconclusive or not interpretable will be considered non-compliant.

The Clinical trials should be performed in accordance with Good Clinical Practice. Those conducted outside the community should be carried out in accordance with the ethical standards of Directive 2001/20/EC and those conducted within the community should be carried out in accordance with Directive 2001/20/EC.

Applicants are reminded that it is their responsibility to submit a request for modification of an agreed paediatric investigation plan, if they encounter difficulties with its implementation which render the plan unworkable or no longer appropriate.

Applicants are also reminded that in order to verify compliance with the agreed PIP, the final study report must be submitted (Commission Guideline 2008/C243/01 of 24 September 2008) for any study that had to be completed. This is part of the validation of the application for marketing authorisation, variation or line extension. Applicants are therefore advised to consider the time necessary to produce the final report for their planned date of submission. For authorised medicinal products, the report needs to be submitted within 6 months of completion of the study according to article 46 of Regulation (EC) No 1901/2006.