EMA/226610/2024

European Medicines Agency decision

P/0183/2024

of 17 May 2024

on the agreement of a paediatric investigation plan and on the granting of a deferral and on the granting of a waiver for ganaxolone (ZTALMY), (EMEA-002341-PIP02-23) 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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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 Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency[2],

Having regard to the application submitted by Marinus Pharmaceuticals, Inc. on 24 April 2023 under Article 16(1) of Regulation (EC) No 1901/2006 also requesting a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation,

Having regard to the opinion of the Paediatric Committee of the European Medicines Agency, issued on 26 April 2024, in accordance with Article 17 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, as amended.
[2] OJ L 136, 30.4.2004, p. 1, as amended.

Has adopted this decision:

Article 1

A paediatric investigation plan for ganaxolone (ZTALMY), oral suspension, oral use, gastric 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 ganaxolone (ZTALMY), oral suspension, oral use, gastric 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 ganaxolone (ZTALMY), oral suspension, oral use, gastric 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 covers all conditions, indications, pharmaceutical forms, routes of administration, measures, timelines, waivers and deferrals, as agreed in the decision P/0361/2019 issued on 4 November 2019, including subsequent modifications thereof.

Article 5

This decision is addressed to Marinus Pharmaceuticals, Inc., 5 Radnor Corporate Center 100, Suite 500, PA 19087-4535 – Radnor, United States.

EMA/PDCO/61216/2024 Corr[1]
Amsterdam, 26 April 2024

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

EMEA-002341-PIP02-23

Scope of the application

Active substance(s):

Ganaxolone

Invented name and authorisation status:

See Annex II

Condition(s):

Treatment of tuberous sclerosis complex

Pharmaceutical form(s):

Oral suspension

Route(s) of administration:

Oral use

Gastric use

Name/corporate name of the PIP applicant:

Marinus Pharmaceuticals, Inc.

Basis for opinion

Pursuant to Article 16(1) of Regulation (EC) No 1901/2006 as amended, Marinus Pharmaceuticals, Inc. submitted for agreement to the European Medicines Agency on 24 April 2023 an application for a paediatric investigation plan for the above mentioned medicinal product and a deferral under Article 20 of said Regulation and a waiver under Article 13 of said Regulation.

The procedure started on 22 May 2023.

[1] 15 May 2024

Supplementary information was provided by the applicant on 18 January 2024. The applicant proposed modifications to the paediatric investigation plan and waiver.

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 17(1) 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)(c) of said Regulation, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

   The Paediatric Committee member of Norway agrees 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 annexes and appendix.

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)

Waiver

1.1. Condition:

Treatment of tuberous sclerosis complex (TSC)

The waiver applies to:

- the paediatric population from birth to less than 1 month of age;
- oral suspension, oral use; gastric use
- on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

2. Paediatric investigation plan

2.1. Condition:

Treatment of tuberous sclerosis complex

2.1.1. Indication(s) targeted by the PIP

Adjunctive treatment of seizures in paediatric patients from 1 month of age with tuberous sclerosis complex (TSC)

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

From 1 month to less than 18 years of age

2.1.3. Pharmaceutical form(s)

Oral suspension

2.1.4. Measures

Area	Description
Quality-related studies	**Study 1 (040619GNX & 1042-010 – same studies as in EMEA-002341-PIP01-18-M02)** Development of an age appropriate sodium benzoate-free ganaxolone oral suspension (50 mg/mL)
Non-clinical studies	Not applicable
Clinical studies	**Study 2 (1042-TSC-2001)** Open-label 12-week trial to evaluate safety and activity of adjunctive ganaxolone treatment (Part A) in patients from 2 years to less than 18 years of age (and adults) with tuberous sclerosis complex-related epilepsy, followed by long-term treatment (Part B)

	Study 3 (1042-TSC-3001 - EudraCT 2021-003441-38) Double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone in patients from 1 year to less than 18 years of age (and adults) with tuberous sclerosis complex-related epilepsy **Study 4 (1042-TSC-3002 - EU CT 2022-503067-15-00)** Open-label extension study of adjunctive ganaxolone treatment (up to 3 years) in children from 1 year to less than 18 years of age (adult adults) with tuberous sclerosis complex-related epilepsy who participated in either study 1042-TSC-2001 (Study 2) or study 1042-TSC-3001 (Study 3) **Study 5 (1042-TSC-3003)** Open-label, single-arm 16-week study of adjunctive ganaxolone treatment in paediatric participants from 1 month to less than 2 years of age with clinically- or genetically confirmed tuberous sclerosis complex-related epilepsy (Part A) followed by long-term treatment (Part B) to assess the safety, tolerability, and activity of ganaxolone treatment as adjunctive therapy to the patients' standard anti-seizure medication
Modelling and simulation analyses	**Study 6** Physiologically-based pharmacokinetic (PBPK) model (PB-PK), to predict and confirm the paediatric dose to be used in study 5, in children from 1 month to less than 2 years of age with tuberous sclerosis complex-related epilepsy **Study 7** Population PK study, to evaluate the use of ganaxolone in children from 1 month to less than 18 years of age with tuberous sclerosis complex - related epilepsy
Other studies	Not applicable
Extrapolation plan	Studies 2, 3, 4, 5 are part of an extrapolation plan covering the paediatric population from 1 month to less than 2 years of age, as agreed by the PDCO

3. Follow-up, completion and deferral of PIP

Concerns on potential long term safety/efficacy issues in relation to paediatric use:	Yes
Date of completion of the paediatric investigation plan:	By June 2027
Deferral for one or more measures contained in the paediatric investigation plan:	Yes

Annex II

Information about the authorised medicinal product

Information provided by the applicant:

Condition(s) and authorised indication(s)

1. Treatment of cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder

- Authorised indication(s): ZTALMY is indicated for the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 to 17 years of age. ZTALMY may be continued in patients 18 years of age and older.
  - Invented name(s): ZTALMY
  - Authorised pharmaceutical form(s): oral suspension; white to off-white suspension
  - Authorised route(s) of administration: oral use
  - Authorised via centralised procedure