EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ztalmy (ganaxolone)
Treatment of CDKL5 deficiency disorder
EU/3/19/2224

Sponsor: Marinus Pharmaceuticals Emerald Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance	Ganaxolone
Other names	CCD-1042; Ganaxalone-IV;
International Non-Proprietary Name	Ganaxolone
Tradename	Ztalmy
Orphan condition	Treatment of CDKL5 deficiency disorder
Sponsor's details:	Marinus Pharmaceuticals Emerald Limited 10 Earlsfort Terrace Dublin 2 D02 T380 Co. Dublin Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pharma Gateway AB
COMP opinion	10 October 2019
EC decision	12 November 2019
EC registration number	EU/3/19/2224
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pharma Gateway AB to Marinus Pharmaceuticals Emerald Limited – EC decision of 4 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Armando Genazzani
Applicant	Marinus Pharmaceuticals Emerald Limited
Application submission	9 October 2021
Procedure start	28 October 2021
Procedure number	EMA/H/C/005825
Invented name	Ztalmy
Proposed therapeutic indication	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. Further information on product can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Ztalmy
CHMP opinion	25 May 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Giuseppe Capovilla
Sponsor's report submission	2 November 2021
COMP discussion	15-17 May 2023
COMP opinion (adoption via written procedure)	26 May 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

"The sponsor Pharma Gateway AB submitted on 26 June 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing ganaxolone for treatment of CDKL5 deficiency disorder (hereinafter referred to as "the condition". The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing ganaxolone was considered justified based on preliminary clinical data suggesting a reduction in seizures upon treatment with the proposed product when used in combination with other anti-seizure medications;
- the condition is life-threatening and chronically debilitating due to early-onset pharmaco-resistant seizures, global developmental delay, abnormal muscle tone, hand stereotypies, and gastrointestinal and respiratory problems;
- the condition was estimated to be affecting approximately less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ganaxolone will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting a reduction in seizures upon treatment with the proposed product when used in combination with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing ganaxolone, as an orphan medicinal product for the orphan condition: treatment of CDKL5 deficiency disorder".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

CDKL5 deficiency disorder (CDD) is caused by mutations in the cyclin-dependent kinase-like 5 (CDKL5) gene. The disorder has also other names in the scientific literature including: CDKL5 deficiency, CDKL5 disorder, CDKL5 encephalopathy, CDKL5-related epilepsy, CDKL5-related epileptic encephalopathy, and early infantile epileptic encephalopathy 2.

Initially, CDD was not classified as a separate entity. Instead, patients with mutations in the CDKL5 gene were thought to have had an atypical variant of Rett Syndrome. In 2013, CDD was considered a separate entity from Rett syndrome (Fehr S. et al., 2013), based on a large international cohort of patients with mutations in the CDKL5 gene. The minimum CDD diagnostic criteria to include a pathogenic or likely pathogenic variant in the CDKL5 gene along with motor and cognitive developmental delays and epilepsy with onset in the first year of life (Olson, H.E et al., 2019). It is now considered a developmental and epileptic encephalopathy.

CDKL5 is expressed widely in most tissues, with highest levels in brain, thymus, and testis. Within neurons, it localises in nucleus, neurites, growth cones, dendritic spines, and at the postsynaptic density (PSD) of excitatory synapses. Hector et al (2017) identified more than 200 missense variants of the CDKL5 gene but concluded that, of these, only 59 variants occurring in the catalytic domain were definitely or probably pathogenic. Szafranski et al (2015) have additionally identified a role for CDKL5 duplications in a small number of patients.

The clinical characteristics commonly associated with a CDKL5 mutation include early-onset medication-refractory seizures, severe intellectual and gross motor impairment, and sleep and behavioural disturbances

Most individuals with variants in the CDKL5 gene display a phenotype consisting of early-onset and refractory epilepsy with severe global developmental delay and markedly impaired gross motor function (Fehr 2013). Three stages of seizures in the course of CDKL5 deficiency disorder (CDD) have been proposed: Stage I, early onset epilepsy (onset at 1 to 10 weeks of age); Stage II, epileptic encephalopathy with IS and hypsarrhythmia; Stage III, tonic seizures with myoclonia and variable level of control with anti-seizure medication (ASM) (Bahi-Buisson 2008b). Frequent myoclonic jerks are a key component of the epileptic manifestations at this later stage (Demarest 2019; Bahi-Buisson 2008b). Some patients show an unusual seizure pattern with prolonged generalised tonic-clonic events lasting 2 to 4 minutes gradually transitioning to repetitive, distal myoclonic jerks (Bahi-Buisson 2008b).

Early drug-resistant epilepsy, usually starting in the first months of life, is characteristic of CDD (Bahi-Buisson 2008b). Seizures are generally highly polymorphic, and patients can manifest multiple seizure types (Bahi-Buisson 2008b; Grosso 2007). Patients can often experience a period of seizure freedom, or a "honeymoon period", after initiation of a new ASM (Fehr 2016b). However, this period of seizure-control is frequently short-lived and followed by a relapse (Kilstrup-Nielsen 2012).

CDD, being X-chromosome linked, is more common in females. Male patients have a more severe phenotype.

The approved therapeutic indication "*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*'' falls within the scope of the designated orphan condition "*treatment of CDKL5 deficiency disorder*".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

The sponsor discussed the chronically debilitating nature of the condition with most patients failing to achieve key developmental milestones (sitting, standing, and/or walking) during their early years and in consequence will require round-the-clock support for the rest of their lives (Fehr 2016b). Recently, a study exploring the quality of life of patients with CDD has been published (Leonard 2021). Key disease aspects negatively affecting quality of life included the lack of ability to sit, use hands, or communicate. Less than a quarter of females and fewer males ever achieve the ability to walk (Fehr 2016a; Fehr 2015). Similarly, only a quarter to a third of females are ever able to use any spoken language, signs, and/or abstract symbols (Fehr 2016a; Fehr 2016b).

The sponsor also discussed the life-threatening nature of the condition. The overall life-expectancy of individuals with CDD is likely to be shorter than age matched healthy individuals, although this is not clearly established in the literature. Most patients reported to date have been infants, children, or adolescents, with very limited numbers of patients reported to have survived into their late 30's (Kobayashi 2021; Siri 2021; MacKay 2020; MacKay 2021; Cutri-French 2020; Demarest 2019; Olson 2019). As with any epileptic encephalopathy that affects multiple body systems in the body, as CDD does, there is a higher probability of premature death due to the epilepsy syndrome per se, or other contributing factors like respiratory and GI problems/failure. Unexpected death, most likely due to sudden unexpected death in epilepsy (SUDEP) is a risk for patients with CDD (Jakimiec 2020). Genetic studies have suggested a potential pathogenic role of CDKL5 variants in the cardio-cerebral mechanisms of SUDEP (Coll 2017).

The COMP considers the condition to be life-threatening and chronically debilitating due to early-onset pharmaco-resistant seizures, global developmental delay, abnormal muscle tone, hand stereotypies, and gastrointestinal and respiratory problems.

Number of people affected or at risk

The prevalence has been estimated by using 3 methods presented in Table 1:

1. A birth prevalence estimate was reported by Symonds 2019. This estimate was derived from a Scottish prospective, population-based, national cohort study. Participants were recruited from all 20 regional paediatric departments and four tertiary children's hospitals in Scotland, from 8 May 2014 to 7 May 2017. The mean number of births per year in Scotland for the years 2011 to 2016 inclusive was 56,490, making the estimated denominator for this population 169,470. Four unrelated individuals carrying a CDKL5 mutation were identified, resulting in an estimated birth prevalence of 2.36 (95% CI: 0.805-5.59) per 100,000 live births for the years 2011 to 2016.

2. Point prevalence extrapolated from birth-prevalence: Unfortunately, there is very little information on life-expectancy of patients carrying a CDKL5 mutation; what little data there are come from case reports that suggest affected individuals may, exceptionally, live until approximately 40 years of age. An estimate of point prevalence of CDD in the EEA can be derived from the reported birth prevalence estimates, using the conservative assumption that all patients born with a CDKL5 mutation live to 45 years of age, with a median life expectancy of the European population of 81.3 years in 2019 (Eurostat 2021). Conservatively, from the Scottish and expectation score-derived birth prevalence estimates, the point prevalence estimates for CDD are:

- Scotland: 2.36 (95% CI: 0.805-5.59) × 45/81.3 = 1.31 (0.45-3.09) per 100,000.
- Expectation score: 1.81-2.49 × 45/81.3 = 1.00-1.38 per 100,000.

3. Prevalence estimated by extrapolation from diagnostic yield of CDKL5 mutations in patients assumed to have Rett syndrome but no identified MECP2 mutation: The overall weighted-average proportion of CDKL5 mutations amongst typical/atypical Rett patients is estimated to be 0.04 (95% CI 0.03, 0.06).

Table 1. Estimated prevalence of CDD in the EEA

Method	**Source**	**Prevalence estimate per 10,000a**	**Estimated number with CDD in EEA (EU27+3)b**
Birth prevalence – no adjustment for early mortality	Scotland	0.2 (95% CI: 0.1-0.6)	9,056 (4,528-27,168)
	Expectation score	0.2-0.3	9,056-13,584
Birth prevalence – adjusted for early mortality	Scotland	0.1 (95% CI: 0.05-0.3)	4,528 (2,260-13,584)
	Expectation score	0.1-0.1	4,528
Based on CDKL5 mutation yield in all Rett patients	Meta analysis	0.04	1,811

Sources: Scotland = Symonds 2019; Expectation score = López-Rivera 2020; Meta analysis = Figure 10
a Rounded to 1 significant figure from data per 100,000 described above
b Number = maximum prevalence × 452,806,812/10,000

In conclusion, there are currently no population based epidemiological data of CDKL-5 deficiency disorder, except for the study limited to the region of Scotland. The presented indirect methods, which estimated prevalence from population-based sources on Rett syndrome, are considered acceptable. In the future, genotyping may become more common in daily practice, and more carriers may be diagnosed. In light of the highlighted uncertainty, it seems adequate to consider the most conservative estimate and to designate less than 0.6 per 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor highlighted that there are no ASMs (anti-seizure medications) authorized specifically for the treatment of CDD. Seizures associated with CDD, which are characteristically refractory, are managed with a wide range of ASMs of limited effectiveness (Müller 2016), and various non-pharmaceutical interventions including the ketogenic diet, VNS and, in some cases, neurosurgical treatment (Olson 2019; Jakimiec 2020).

There are not yet international consensus treatment guidelines for CDKL-5 disorder. There is a recent treatment guideline from the French Haute Autorité de Santé (2021), which recommends vigabatrin as a first-line treatment for infantile spasms associated with CDD and mentions broad-spectrum anti-epileptic drugs such as felbamate, clobazam, valproate sodium, lamotrigine, and zonisamide for generalised seizures. In addition, non-pharmacological options such as a ketogenic diet (limited added value) and surgical interventions can also be considered. Seizures may be treated symptomatically with anticonvulsants. Use of ketogenic diet is reported to have early efficacy but poor long-term efficacy in controlling seizures in CDKL5 deficiency disorder. The use of vagus nerve stimulation for seizure control has been reported in 17% of patients.

Corpus callosotomy, a palliative procedure in which hemispheric connections are severed to limit seizure spread, is a treatment of last resort, which can occasionally offer seizure control of secondary generalised seizures (Olson 2019).

There is no standard-of-care for the treatment of the behavioural aberrations associated with the encephalopathy.

The COMP considered that there are no authorized medicinal products available in the EU that are specifically indicated for the treatment of seizures associated with CDKL5, however, the anti-seizure medications used as standard of care to manage the seizures are considered as satisfactory methods to treat seizures in CDD and will be discussed further under significant benefit section below.

Significant benefit

The sponsor claimed the significant benefit on the basis that ganaxolone, when added to a background regimen of ASMs and/or other non-pharmacological therapies (ketogenic diet or VNS), provides a clinically relevant advantage in terms of improved efficacy (with acceptable safety) over those same ASMs alone.

The efficacy to treat seizures associated with CDD in paediatric patients 2 years and older was confirmed in a single, double-blind, randomised, placebo-controlled study of 17 weeks in patients aged 2 to 19 years (Study 1042- CDD-3001). The blinded study consisted of a titration phase of 4 weeks, followed by a maintenance phase of 13 weeks using a stable dose of the study drug. Subjects were required to continue their concomitant background ASM regimen at constant dose for the duration of the 17week DB period of the Phase 3 study. Patients were eligible for Study 1042-CDD-3001, if they had a molecular confirmation of pathogenic or likely pathogenic CDKL5 variant, their seizures were inadequately controlled by at least 2 previous concomitant ASM medicinal products, and they had a

minimum of 16 seizures of primary seizure type per 28 days in each 1-month period during the 2-month period prior to screening.

In total, 101 patients were enrolled into the study (51 placebo and 50 ganaxolone (GNX)). Patients were mostly female (79.2%; consistent with the demographics of CDD) and aged between 2 and 19 years (mean [standard deviation (SD)]: 7.26 [4.55]) with the majority being paediatric (children 2 to 11 years [82.2%], adolescents [16.8%]). Concomitant ASMs were given to 96% patients. The median number of concomitant ASM medicines used by subjects was 2 (range 0-5) in the placebo group and 2 (range 0-6) in the Ztalmy group. The median number of ASM taken and stopped prior to treatment for all subjects was 7 (range: 1 to 16). The most frequent (≥ 10 patients) concomitant ASM medicines were valproate, levetiracetam, clobazam and vigabatrin (see Table 3).

The primary efficacy endpoint was the percentage change from baseline in 28-day frequency of major motor seizures (i.e. bilateral tonic (sustained motor activity ⩾ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures and focal to bilateral tonic-clonic seizures)) during the 17-week double blind treatment phase. At baseline, the mean (SD) number of major motor seizures over 28-days was 104.8 (173.53) for placebo and 117.2 (138.62) for Ztalmy. The median number of seizures were 49.2 (Q1, Q3 18.7, 120.0) in the placebo group and 54.0 (31.3,147.3) at baseline.

There was a broadly comparable frequency of use of each individual ASM across the two treatment arms, and especially so for the four most taken concomitant ASMs (Table 2).

Table 2. ASM medications during 17-week DB period (3001, Safety Population)

ASM medications	**Placebo N=51 n (%)**	**Ganaxolone N=50 n (%)**	**Total N=101 n (%)**
Any	48 (94.1)	49 (98.0)	97 (96.0)
Valproate semisodium	16 (31.4)	18 (36.0)	34 (33.7)
Levetiracetam	13 (25.5)	13 (26.0)	26 (25.7)
Clobazam	13 (25.5)	12 (24.0)	25 (24.8)
Vigabatrin	12 (23.5)	10 (20.0)	22 (21.8)
Topiramate	8 (15.7)	6 (12.0)	14 (13.9)
Zonisamide	6 (11.8)	7 (14.0)	13 (12.9)
Clonazepam	4 (7.8)	6 (12.0)	10 (9.9)
Lamotrigine	6 (11.8)	4 (8.0)	10 (9.9)
Rufinamide	5 (9.8)	6 (12.0)	11 (10.9)
Phenobarbital	3 (5.9)	4 (8.0)	7 (6.9)
Perampanel	3 (5.9)	3 (6.0)	6 (5.9)
Felbamate	4 (7.8)	1 (2.0)	5 (5.0)
Nitrazepam	2 (3.9)	3 (6.0)	5 (5.0)
Diazepam	1 (2.0)	3 (6.0)	4 (4.0)
Lacosamide	3 (5.9)	1 (2.0)	4 (4.0)
Midazolam hydrochloride	2 (3.9)	2 (4.0)	4 (4.0)
Ethosuximide	1 (2.0)	2 (4.0)	3 (3.0)
Gabapentin	1 (2.0)	2 (4.0)	3 (3.0)

Oxcarbazepine	0	3 (6.0)	3 (3.0)
Brivaracetam	0	2 (4.0)	2 (2.0)
Carbamazepine	1 (2.0)	1 (2.0)	2 (2.0)
Phenytoin	2 (3.9)	0	2 (2.0)
Sultiame	1 (2.0)	1 (2.0)	2 (2.0)
Cannabidiol	1 (2.0)	1 (2.0)	2 (2.0)
Chloral hydrate	0	1 (2.0)	1 (1.0)
Immunoglobulins NOS	0	1 (2.0)	1 (1.0)
Lorazepam	0	1 (2.0)	1 (1.0)
Medroxyprogesterone acetate	1 (2.0)	0	1 (1.0)
Pyridoxine	0	1 (2.0)	1 (1.0)
Stiripentol	1 (2.0)	0	1 (1.0)

NOS = Not otherwise specified

At the end of the 13-week maintenance phase, there was a statistically significant difference in the median percent change from baseline in major motor seizure (MMS) frequency for patients treated with Ztalmy compared to patients receiving placebo of -27% (95% CI: -47.9, -9.6) (Table 3).

Table 3. Summary of median percentage change from Baseline in 28-day seizure frequency for major motor seizure types during 17week double blind period by concomitant ASM

Concomitant ASM	**Median (95% Distribution-free CI) % change from Baseline**		**Hodges-Lehmann estimate of location shift (95% CI)[a]**	**Wilcoxon Test p-value**
	Placebo	**Ganaxolone**		
Overall	N=51	N=50		
	-6.90 (-16.47, 15.34)	-30.66 (-35.94, -11.98)	-27.08 (-47.92, -9.55)	0.0036
Valproate semisodium	N=16	N=18		
	-0.15 (-20.32, 39.66)	-36.46 (-65.03, -16.77)	-46.09 (-78.20, -13.37)	0.0075
Levetiracetam	N=13	N=13		
	-16.47 (-33.68, 12.50)	-31.97 (-43.46, 14.39)	-14.19 (-37.34, 13.17)	0.1824
Clobazam	N=13	N=11		
	12.50 (-21.11, 39.66)	-40.89 (-60.91, -23.46	-53.39 (-83.12, -28.13)	0.0014
Vigabatrin	N=12	N=10		
	6.86 (-21.66, 59.29)	-10.03 (-35.94, 51.84)	-15.91 (-76.84, 19.35)	0.3734

Clinical relevance is supported by responder analyses (>= 50% reduction of MMS frequency from baseline at Week 17), which was 24.5% for GNX and 9.8% for placebo (difference 14.7%, 95% CI -4.7, 33.8, p-value (Fisher exact test) 0.0643).

Furthermore, in different subgroups of the four most commonly used ASM in the study population, in the in general balanced treatment arms, there was a tendency that ganaxolone provided a shift in MMS as compared to placebo, supporting the robustness of the treatment effect (see Table 3 above). Since the subgroups based on background ASM were small, statistical significance was not always achieved for each subset. However, efficacy can be considered shown for the whole target population,

independent from the background therapy, as the data from the subsets all pointed at the same positive direction for GNX.

According to the sponsor, a reduction in median 28-day seizure frequency for MMS types of -27% and reductions relative to 'standard of care' ASM regimens including valproate semisodium, levetiracetam, clobazam, and/or vigabatrin of between 16% and 53% represent a clinically relevant advantage over existing satisfactory methods. Furthermore, the sponsor claims that data from the on-going open-label extension of the Phase 3 study support that ganaxolone at least retains a similar level of efficacy in reducing seizure frequency for MMS types over a period of up to 24 months. From the originally randomised 101 subjects, 48 (48%) who have already completed month 11-12 visits in the open-label extension experienced a median 50% reduction from Baseline in 28-day seizure frequency for MMS types. This in contrast to what has been reported previously for other treatments in a study by Müller 2016, which suggests that no other ASM remains similarly effective over a period of time of more than 6 months. However, due to the retrospective and non-randomised nature of the study by Müller (2016), and the small sample size, the COMP considered that no clear conclusions can be drawn regarding the duration of response from this study. Moreover, it is unclear whether the study populations were comparable.

The COMP considered that that the statistically significant reduction in major motor seizures, in favour of ganaxolone treatment in patients who had a history of failure to control seizures despite an appropriate trial of 2 or more anti-seizure medications at therapeutic doses can justify the significant benefit. The claim of a better maintenance of efficacy is not considered acceptable based on the ongoing uncontrolled phase of the study. In conclusion, the COMP concluded that the significant benefit is justified based on the significant reduction of seizures, as shown in patients who received ganaxolone an adjunctive therapy to standard of care.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 26 May 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of CDKL5 deficiency disorder (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to early-onset pharmaco-resistant seizures, global developmental delay, abnormal muscle tone and hand stereotypies. A reduction of life expectancy is mainly due to respiratory complications;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Ztalmy, the assumption that Ztalmy will be of significant benefit to those affected by the orphan condition when it is used as an adjunctive therapy to standard of care still holds.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ztalmy, ganaxolone for treatment of CDKL5 deficiency disorder (EU/3/19/2224) is not removed from the Community Register of Orphan Medicinal Products.