EU Risk Management Plan
for
Ztalmy

(Ganaxolone 50 mg/mL suspension)

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List of Abbreviations

Abbreviation/Term	Definition
ACTH	Adrenocorticotropic hormone
ADAMS	Anxiety, depression, and mood scale
AED	Anti-epileptic drug
AESI	Adverse event of special interest
Allo-S	Allopregnanolone-sulfate
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the plasma concentration-time curve
β-CD	β-cyclodextrin
BID	Two times a day
BMI	Body mass index
CBD	Cannabidiol
CDD	Cyclin-dependent kinase-like 5 deficiency disorder
CDKL5	Cyclin-dependent kinase-like 5
CGICA	Caregiver global impression of change in attention
CGI-C	Caregiver global impression of change
CGI-I	Clinical global impression of improvement
CGI-CSID	Caregiver global impression of change in seizure intensity/duration
CI	Confidence interval
C_{max}	Maximum concentration
CNS	Central nervous system
CSHQ	Children's sleep habit questionnaire
CSR	Clinical study report
C-SSRS	Columbia suicide severity rating scale
CYP	Cytochrome P
DDI	Drug-drug interaction
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
E_{max}	Maximum effect
EPAR	European Public Assessment Report

Abbreviation/Term	Definition
EU	European Union
F_1	First generation offspring
GABA	Gamma-aminobutyric acid
$GABA_A$	Gamma-aminobutyric acid type A
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP	Good laboratory practice
GNX	Ganaxolone
hERG	Human ether-à-go-go-related gene
IB	Investigator Brochure
ICDD	International CDKL5 disorder database
ICH	International council for harmonisation of technical requirements for pharmaceuticals for human use
ILAE	International league against epilepsy
IS	Infantile spasms
kD	Kilodalton
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
NOAEL(s)	No observed adverse effect level(s)
NOEL	No observed effect level
NORD	National organisation for rare diseases
PCDH19	Protocadherin 19
PK	Pharmacokinetic
PL	Patient leaflet
PRO	Patient reported outcome
PSI	Parenting stress index
QI-Disability	Quality of life inventory-disability
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of product characteristics
SMRC	Scientific and medical review committee

Abbreviation/Term	Definition
SUDEP	Sudden unexpected death in epilepsy
TEAE	Treatment emergent adverse events
THC	Tetrahydrocannabinol
TID	Three times a day
TK	Toxicokinetic
tmax	Time to reach maximum concentration
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organisation
WoE	Weight of Evidence

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Ganaxolone
Pharmacotherapeutic group(s) (ATC Code)	Antiepileptics, other antiepileptics (ATC code: N03AX27).
Marketing Authorisation Applicant	Marinus Pharmaceuticals Emerald Limited
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	ZTALMY®
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Neurosteroid; a methyl substituted analogue of the endogenous neurosteroid allopregnanolone, a derivative of progesterone.
	Summary of mode of action: Ganaxolone (GNX) has the same core structure as allopregnanolone, but with the addition of a 3β-methyl group to prevent enzymatic conversion to an entity (i.e., 3-keto) active at nuclear progesterone receptors. GNX is a neuroactive steroid that positively and allosterically modulates gamma-aminobutyric acid type A ($GABA_A$) receptors in the central nervous system (CNS) by interacting with a recognition site that is distinct from other allosteric $GABA_A$ receptor modulators. The precise mechanism by which GNX exerts its therapeutic effects in the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is unknown, but its anticonvulsant effects are thought to result from this modulation of $GABA_A$ receptor function providing constant, or tonic, modulation of GABA-mediated inhibitory neurotransmission.
	Important information about its composition: The chemical name for GNX is 3α-hydroxy-3β-methyl-5α-pregnan-20-one ($C_{22}H_{36}O_2$) with a molecular weight of 332.53 kD. It is a neutral hydrocarbon molecule. The oral suspension of GNX has a shelf life of 2 years.
Hyperlink to the Product Information	ZTALMY Product Information (Module 1.3.1)
Indication(s) in the EEA	Current: 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.
	Proposed: Not applicable

Dosage in the EEA	Current: The maximum recommended daily dose is 63 mg/kg/day for patients weighing ≤28 kg or 1,800 mg/ day for patients weighing >28 kg, following an initial titration schedule over 4 weeks. Total daily dose is administered in 3 separate doses (every 8 hours).
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: An oral, white to off-white suspension. Each 1 mL suspension contains 50 mg GNX.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

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.

Incidence and prevalence

CDD is classed as a rare disease with an estimated global prevalence of 1:42,000 (CDKL5 UK 2021, LouLou Foundation, 2021). The exact prevalence of cyclin-dependent kinase-like 5 (CDKL5) mutations in the European Union (EU) is currently unknown. Mutations in CDKL5 are estimated at approximately 1 in 40,000–60,000 live births (Jakimiec 2020; Olsen 2019, Demarest 2019).

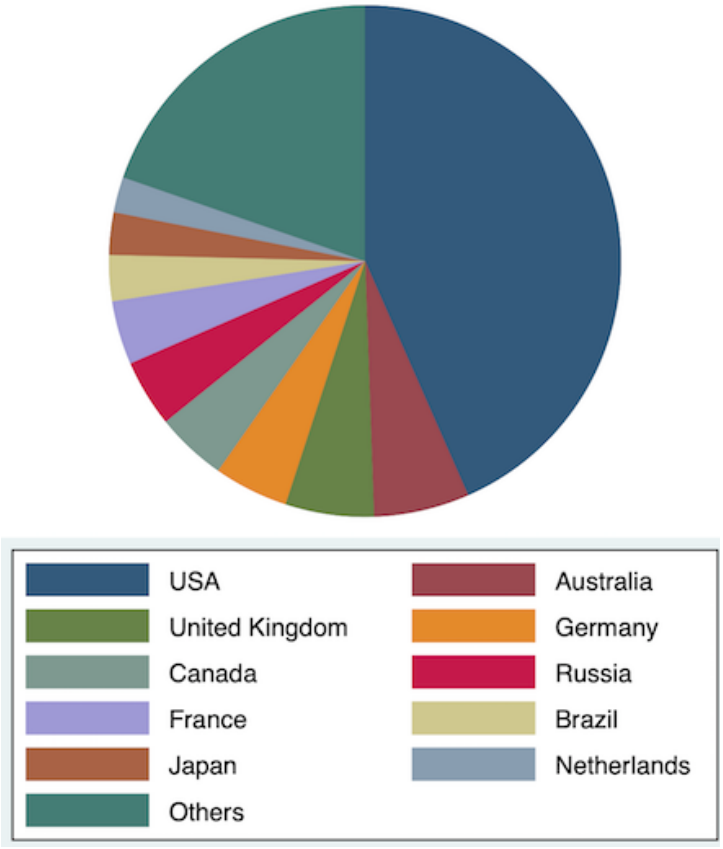
An estimate for birth prevalence of CDD in Australia was published in 2017 based on an analysis of data from the International CDKL5 Disorder Database (ICDD) (Hector 2017). These authors suggest a lower estimate of birth prevalence in Australia of 0.21 cases per 100,000 live births (95% CI 0.12–0.33) for the years 1982 to 2014. However, these authors cautioned that, whilst a birth prevalence in this range would indicate that CDKL5 deficiency is an ultra-rare disorder, it was likely that this figure would increase as targeted next-generation sequencing for investigation of early-onset epileptic encephalopathy becomes more common and more families contribute to the database. Indeed, the frequency of patients diagnosed with CDD is already increasing due to growing awareness of the disorder and the inclusion of CDKL5 in routine genetic testing of early epileptic encephalopathies (Gokben 2017). In 2016, the LouLou Foundation was aware of over 1,200 documented cases worldwide (LouLou Foundation, 2021).

A study conducted in the United Kingdom recruited 343 children presenting with epilepsy under the age of 3 years between May 2014 and May 2017 from all 20 regional paediatric departments and four tertiary children's hospitals in Scotland. Four unrelated cases of CDKL5 epilepsy were identified from the 333 patients who completed genetic testing (4/333; 1.2%), giving an annual incidence of 1 per 42,400 live births (2.36/100,000 [95% CI, 0.805-5.59]; Symonds 2019). A population-based approach was taken to avoid selection bias with broad inclusion criteria and proactive recruitment strategy, although a small cohort was assessed and only considered patients aged <3 years. An earlier study was conducted in the US on 8565 individuals with epilepsy and/or neurodevelopment disorders over a 4-year period from December 2011 to December 2015. Genetic diagnosis was positive in 1315 cases, from which 99 cases of CDKL5 epilepsy were identified (99/1315; 7.6%), with patient age at molecular diagnosis ranging from 0.1 – 31.1 years (mean age 3.3 years, median age 1.8 years) (Lindy 2018).

A distribution of cases by country of residence, based on data in the ICDD, is publicly available (Figure 1). Based on this breakdown, roughly 25% of cases in the ICDD are in EU27+3 countries, although the extent of reporting to this database from EU countries is not known. Prevalence estimates based on this type of data are likely to suffer from ascertainment bias, as well as bias due to variable availability of routine next-generation genetic testing for early onset epileptic encephalopathy (Mangatt 2016). Furthermore, CDKL5 has only recently been included

in the panel of genes screened for mutations. Many historical cases are likely to remain misclassified, and/or are included in the RettBASE database (RettSyndrome.org Variation Database: http://mecp2.chw.edu.au/) instead of, or in addition to ICDD. As of June 5, 2016, there were 498 cases of CDD recorded in RettBASE (Krishnaraj 2017).

Figure 1: Distribution of CDKL5 Deficiency Disorder Cases by Country of Residence: Cases in the ICDD



Others: Argentina, Belarus, Belgium, Bulgaria, Chile, China, Denmark, Finland, Georgia, Greece, Hungary, India, Indonesia, Ireland, Israel, Italy, Jordan, Kazakhstan, Korea, Luxembourg, Malaysia, Mexico, New Zealand, Norway, Peru, Poland, Portugal, Romania, Saudi Arabia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine.

Source: International CDKL5 Disorder Output Database, 2021 (http://cdkl51.childhealthresearch.org.au/)

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

CDD is a developmental and epileptic encephalopathy with onset early in life (median age of 6 weeks) with 90% beginning by 3 months (Olsen 2019), caused by a mutation in the catalytic domain of the *CDKL5* gene (Fehr 2013). The *CDKL5* gene is located on the X chromosome; the majority of CDD patients are heterozygous females carrying missense, nonsense, splice, or frameshift *CDKL5* gene mutations, or a genomic deletion (Bahi-Buisson 2011; Fuchs 2018). Boys carrying mutations in *CDKL5* are much rarer (Mangatt 2016; Amendola 2014; Fehr 2013) and show more severe epileptic encephalopathy than girls (Fehr 2016; Fehr 2015; Mirzaa 2013), probably due to the more severe consequences of dominant X-linked mutations in males than in females. CDKL5 mutations have been identified in many ethnic groups, with more females than males being reported with an approximate ratio of 4:1 (NORD 2020).

Other risk factors include a family history of CDKL5 mutations. This is probably the effect of germline mosaicism in one of the parents, such that the offspring can inherit the mutated gene; the frequency of mosaicism variants being estimated at about 8.8% of CDDs (Jakimiec 2020).

The main existing treatment options

There is currently no targeted therapy available to solve the underlying problem related to CDD (Wilcox 2020). Treatments are symptomatic and directed at the most disabling consequences of the disorder. Additional care may be provided through physiotherapy, occupational therapy, neurological speech therapy, and dietetics (Bahi-Buisson 2011, Jakimiec 2020).

Eighty percent of children with CDD have daily seizures and 20% have weekly to monthly seizures (Olsen 2019). Current treatment methods for CDD-related seizures include anti-epileptic drugs (AEDs), ketogenic diet, vagal nerve stimulation, neurosurgery, and steroid treatment (International Foundation for CDKL5 Research 2014). In the case of AEDs, none is specifically indicated for the treatment of CDD, and all are incompletely effective as chronic treatments, with a few of the more effective AEDs leading to seizure control lasting only a few weeks to a few months. An international survey of current practice in CDD was conducted amongst 47 experts, including 30 paediatric neurologists, 10 epileptologists, and 2 geneticists, as well as a general paediatrician, a development/community paediatrician, and an allied health professional. Two of the 47 respondents did not describe their specialty. The aim of the survey was to provide consensus guidance for the delivery of best clinical care. There was no consensus for any of the first, second, third, or fourth line suggested therapies for epileptic spasms associated with CDD although consensus recommendation was identified for GNX and cannabidiol (CBD) to be offered if clinically indicated (Amin 2022).

Although existing licensed AEDs (ILAE 2021; Glauser 2013) are used to treat CDD, they have limited efficacy in this condition. In one cohort of 86 patients derived from the International Rett Syndrome patient registry and database (InterRett), overall control of seizures was poor, with 52/72 (72%) females and 8/9 (89%) males having daily seizures, 5/72 (7%) females having weekly seizures, and 10/72 (14%) females and 1/9 (11%) males having monthly seizures. Only 5/72 (7%) females had experienced no seizures in the last year (Fehr 2013). A larger cohort with seizure information (n=137) from the ICDD (which may partially overlap the InterRett database) also suggests a poor therapeutic outcome with current therapies. Ninety-five patients (69.3%) were experiencing seizures daily, on average between 1 and 21 seizures/day, 19 (13.9%) experienced weekly seizures, 13 (9.5%) experienced monthly seizures, and 1 (0.7%) experienced occasional seizures. Only 9 (6.6%) individuals were seizure free for >1 year (Mangatt 2016). These publications suggest poor seizure control; however, neither explicitly characterises the range of therapeutic interventions these cohorts of CDD patients were or had been receiving.

A retrospective review of 39 CDD patients (34 females; age 0.6-22.4 years; mean 7.3 years; median 5.8 years) who had gone through a multitude of AED treatments, including the ketogenic diet, illustrates the generally poor treatment response (Müller 2016). Patients were treated with 3 to 21 (mean 9; median 9) AEDs, most commonly valproic acid (87%), levetiracetam (79%), topiramate (79%), steroids (67%), phenobarbital (67%) and vigabatrin (64%); 31% undertook a ketogenic diet. A responder rate (defined as 50% seizure reduction) to at least one AED of 69% was observed at 3 months, 45% at 6 months, falling to 24% at 12 months. Medications with the highest rates of seizure reduction at 3 months included felbamate, vigabatrin, clobazam, valproic acid, steroids, lamotrigine and zonisamide. At 12 months, the responder rate dropped to 0–20% except for 1/3 (33%) still responding to felbamate. Only 2 patients became seizure free: one with carbamazepine for 10 years, and another with vigabatrin plus phenobarbital for 3 years. In all other patients, seizures reoccurred within weeks to months of initiating a new AED. Most patients

showed transient responses of varying degrees to AEDs with different modes of action, which was typically lost 3 months following the AED regimen change. Currently, there is no disease-specific AED regime available with long-term efficacy in patients with CDD (Müller 2016).

Despite the availability of many new AEDs with differing mechanisms of action, overall outcomes in newly diagnosed epilepsy have not improved. A longitudinal observational cohort study was conducted at the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland on 1795 individuals who were newly treated for epilepsy with AEDs between July 1982 and October 2012. Individuals were followed up for a minimum of 2 years (until October 2014) or until death, whichever came sooner. During the first decade of the study, the most prescribed drugs were carbamazepine, valproate and phenytoin. By the final decade, the predominant AEDs were valproate, levetiracetam and lamotrigine. Most patients who attain control do so with the first or second AED. The probability of achieving seizure freedom diminishes substantially with each subsequent AED regimen tried. More than one-third of patients experience epilepsy that remains uncontrolled (Chen 2018).

Cannabidiol (CBD; EPIDYOLEX® SmPC) is authorised in Europe for the adjunctive treatment of seizures in patients from 2 years of age with Lennox-Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex. Studies have also been conducted on the effectiveness of cannabidiol therapy in patients with mutations in the *CDKL5* gene and other genetic epileptic encephalopathies. In an open-label interventional trial of 17 CDD patients, the median convulsive frequency decreased from baseline by 41% after 12 weeks of therapy (n=11, interquartile range [IQR]:3-65%) and by almost 60% after 48 weeks of treatment (n=10, IQR:5-75%). The decrease in seizure frequency at baseline (66.4 [n=17], IQR: 25.9–212.0) to that at Week 12 (35.8 [n=11], IQR: 8.9–141.6) was statistically significant (p=0.032). The percentage of responders (≥50%) was 41% at Week 12 and 53% by Week 48 (Devinsky 2018).

Other treatment approaches in CDD that can be used as adjuncts to AEDs include the ketogenic diet, vagal nerve stimulation, steroids including adrenocorticotropic hormone (ACTH), and neurosurgery (International Foundation for CDKL5 Research 2014). The ketogenic diet has modest efficacy in treating epilepsy in CDD (Olsen 2019). A cohort of 104 individuals with CDD treated with a ketogenic diet were studied; median duration of ketogenic diet use was 17 months and positive seizure effects were observed in 58.7% (61/104) (Lim 2017). Of the 61 individuals with positive effects, 49 (80%) reported improvement in seizure frequency, 31 (51%) in seizure duration, and 37 (61%) in seizure intensity. However, compared to those who had never been on the ketogenic diet, the seizure rates were slightly higher in those currently on the diet (incidence rate ratio [IRR] = 1.20, 95% CI = 0.75–1.93) after adjusting for gender, variant group, presence of seizure-free period, and duration of epilepsy. At ascertainment, only 33 individuals (32%) remained on the diet; the most common reason cited for discontinuing the ketogenic diet (in 70 individuals) was the lack of long-term efficacy (51%), followed by severe side effects (26%) (Lim 2017).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The primary symptoms of CDD include early-onset epilepsy (mostly drug-refractory), generalised hypotonia, neurodevelopmental disability, and cortical vision disorders. Several accompanying symptoms are observed, such as autistic features (poor social interactions, poor eye contact), hand stereotypies, gastrointestinal (GI) and orthopaedic abnormalities, or dysmorphic facial features. Despite extensive studies the correlation between the type or location of the mutation and the severity of symptoms cannot be clearly determined (Jakimiec 2020).

Epileptic seizures are usually the first symptom of CDD; the first seizure episodes occurring in 96.9% of patients in the first six months of life and in 90% in the first three months of life (Jakimiec 2020; Mangatt 2016). A 3-stage progression has been reported consisting of early epilepsy (stage 1), followed by infantile spasms (stage 2) and, finally, multifocal and refractory myoclonic epilepsy (stage 3) (Bahi-Buisson 2011). Early diagnosis may have a considerable impact on the quality of life of patients and their families, as well as on psychomotor and intellectual development. Retardation of psychomotor development and intellectual disability affects all patients with CDD (Jakimiec 2020), with an IQ <40 in all 19 CDD patients with a documented IQ score as identified in the Rett Networked Database (Frullanti 2019). The impairment seems to be more related to speech and fine motor skills than achievements in gross motor skills. Brain magnetic resonance imaging (MRI) demonstrates nonspecific abnormalities of varying severity, often showing cortical atrophy and hyperintensities in the white matter of the temporal lobe (Bahi-Buisson 2011). Neuroimaging therefore has limited use for diagnosis, differentiation, or prognosis in CDD.

Due to the rarity of CDD, very little is known about long-term prognosis and life expectancy. Most individuals who have been identified are under 18 years of age; it is often difficult to identify older children and adults due to the frequent lack of complete infant and childhood developmental records and less frequent genetic testing in older individuals.

Important co-morbidities

The establishment of the ICDD has provided opportunity to examine the prevalence of comorbidities of CDD, such as epilepsy, GI problems including feeding difficulties, sleep and respiratory problems and scoliosis. In 167 individuals with the disorder, at least one episode of GI dysfunction was experienced by 86.5% patients, with 71% of patients affected by constipation, 64% with gastroesophageal reflux disease, and 27% experiencing aerophagia (Mangatt 2016). Gastrointestinal disorders are 3.5 times (p=0.02) more prevalent in patients over 10 years of age compared to children under 5 years. Feeding difficulties were reported for 51% of the orally fed individuals with 60% of the children over 2 years of age completely dependent on their families and carers for eating and drinking. A fifth of affected individuals were exclusively enterally fed (gastrostomy tube or nasogastric tube feeding). The majority (86.5%) of individuals were reported to have experienced a sleep problem during their lifetime with current night waking occurring in 58.5%. Almost one-third (32.5 %) were reported to have breathing irregularities at the time of registration, including hyperventilation (13.6%) and breath holding (26.4%). A history of pneumonia was reported for 21.4% and aspiration for 22.6%. The risk of developing scoliosis increased with age with a 68.5% (95% CI 0.53, 0.80) likelihood of developing scoliosis by age 10 years. In comparison to other comorbidities, scoliosis was the least frequently observed and has been rarely reported previously in the literature, possibly due to the younger age distributions in earlier studies since this is a comorbidity that develops over time (Mangatt 2016).

An earlier study of 86 individuals with a CDKL5 mutation identified through the InterRett database (Fehr 2013) observed that CDD patients present with a subtle dysmorphism. Frequently observed facial phenotypic features included a prominent and/or broad forehead (74%), deep-set but ‘large’-appearing eyes (73%), full lips/everted lower (67%), and well-defined philtrum (61%). Fingers in young children are often tapered with proximally puffy fingers/prominent proximal interphalangeal joint observed in 42% and hallux vagus observed in 25% (Fehr 2013).

Overall, the likelihood of experiencing epilepsy, GI problems, respiratory problems, and scoliosis increased with age and males were more vulnerable to respiratory and sleep problems than females. There was no clear relationship observed between mutation group and prevalence of comorbidities (Mangatt 2016).

With any epileptic syndrome that affects multiple systems in the body, as CDD does, there is a higher possibility 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 also a risk for patients with CDD (Jakimiec 2020).

Part II: Module SII - Non-clinical part of the safety specification

A comprehensive nonclinical programme evaluated the safety of GNX in safety pharmacology, PK, and reproductive and developmental toxicity (including juvenile toxicity) studies in rats, mice, and dogs. The key safety findings from non-clinical studies were 1) CNS-related findings (sedation effects) in adult and juvenile animals; 2) cardiovascular findings 3) prolonged pregnancies and dystocia; and 4) delayed sexual maturation in juvenile animals. A brief description of these findings and their clinical relevance is provided below.

CNS-related findings (sedation effects) in adult and juvenile animals

Findings common to all repeat-dose toxicology studies in mice, rats, and dogs were CNS-related clinical signs. The sedation effects were reversible; dose dependent in both incidence and severity; and followed a predictable pattern. The CNS effects tended to be most severe within the first few hours after a daily dose was administered, particularly in the first week of dosing. At lower doses, the CNS effects resolved by the next daily dose, suggesting a C_{max} driven effect, and abated with duration of administration, suggesting tolerance to the sedation effects over time. At high doses, the sedation effects were accompanied by clinical signs of bodies being cold to the touch, tremors and/or laboured respiration. The sedation effects observed in the toxicology studies are consistent with the findings in the modified Irwin test (Study 8396690) and the other non-GLP CNS Safety Pharmacology studies (rotarod, locomotor, and cognitive function) conducted with GNX. The sedation effects observed following GNX administration were attributed to the exaggerated pharmacology of GNX, a positive modulator of $GABA_A$ receptors (2.4 Nonclinical Overview).

Similar to findings in nonclinical studies, the adverse events of somnolence and sedation reported in clinical studies appeared early in treatment, were dose related, and in some cases diminished with continued treatment. In the CDD pivotal study (Study 1042-CDD-3001), somnolence and sedation were reported with a higher incidence in GNX-treated subjects (34.0% and 6.0%, respectively) compared with placebo-treated subjects (5.9% and 3.9%, respectively). CNS-related clinical signs, such as sedation, are a known risk for humans. The SmPC warns that Ztalmy causes somnolence and sedation and use with other CNS depressants, including concomitantly used anti-seizure medicinal products, could potentiate the somnolence and sedation effect. Patients should be advised not to drive or use machines (see SV.1.1).

Cardiovascular findings

There were no changes in QTc intervals, blood pressure parameters, or histopathologic correlates. GNX did not inhibit human ether-à-go-go-related gene (hERG) channels at a concentration of 10 µM (Study 1245-007). In the 12-month repeat-dose toxicology study in dogs (Study 1245-011), a dose-dependent increase in heart rate at ≥3 mg/kg/day (similar to clinical exposure levels) was observed and there were incidences of sinus tachycardia at higher doses. In a GLP-compliant safety pharmacology study in conscious, telemetered beagle dogs (Study 1245-008), there were no alterations in heart rate, or qualitative or quantitative ECG parameters attributed to GNX. The NOEL for the cardiovascular endpoints was the highest dose tested, 15 mg/kg (2.4 Nonclinical Overview).

Sinus tachycardia in the 12-month dog study was noted at C_{max} values that are 8 to 10-fold higher than demonstrated C_{max} values in human subjects, which lowers the potential for these findings to occur in the clinical setting (2.4 Nonclinical Overview). Overall, nonclinical safety studies suggest that GNX is unlikely to have significant cardiovascular safety concerns in humans. No cardiovascular risk has been identified in GNX clinical studies. In a Thorough QT study

(1042-TQT-1001), GNX at maximal concentrations at steady state had no clinically relevant effects on cardiac repolarization or other ECG parameters (2.5 Clinical Overview).

Prolonged pregnancies and dystocia

In the combined embryo-foetal development and pre- and post-natal development study (COY 7/961509) in rats, there was a slight but statistically significant prolongation of gestation at 40 mg/kg/day and 1 female in that dose group showed dystocia. Based on this information, 20 mg/kg/day is considered a reasonable NOAEL for effects of GNX on maternal reproductive function. In first generation offspring (F1), reductions in body weight gain and slight delays in development occurred in the 40 mg/kg/day group, but there were no effects on behaviour or reproductive capacity in the F1 generation as adults. The NOAEL for the study was considered 20 mg/kg/day based on effects on F1 postnatal growth and development.

The reproductive and developmental toxicity studies are of limited value since exposure levels were far below clinically relevant levels. There are limited data on the use of GNX in pregnant women. ZTALMY is not recommended during pregnancy and in woman of childbearing potential not using contraception. Use in pregnancy and during breastfeeding is included as missing information in the RMP.

Delayed sexual maturation in juvenile animals

Two GLP compliant juvenile toxicology studies were conducted in neonatal rats, with dosing starting on prenatal Day 7 and continuing for 7 weeks in the first study (Study COY 2/950920) and 12 weeks in the second study (Study 00398514). The findings between the 2 studies were consistent and demonstrated that responses in juvenile rats were similar to those in adult rats on an AUC exposure basis. A significant delay in attainment of sexual maturation occurred in females, but this did not result in any effects on oestrous cyclicity or fertility or reproductive parameters (2.4 Nonclinical Overview).

There was no observed effect on sexual maturation or clinically meaningful effect on growth (height and weight) in clinical studies with GNX. However, as effects on sexual maturation have a longer latency and need to be followed up for a longer period, “long term safety (including sexual maturation and growth)” is included as a potential risk in the RMP (SVII.3.1.).

Overall, there were no findings in the nonclinical assessment that would preclude the use of GNX in the targeted population.

M2 Metabolite

M2 is a metabolite identified in human subjects administered GNX that contributes between 10% and 20% of total drug-related material in human plasma.

M2 was negative for mutagenicity in the Ames Test at concentrations up to 5000 µg/plate (Study 9603168). However, M2 did elicit statistically significant increases in the incidence of aberrant metaphases in the mammalian chromosome aberration assay at concentrations ≥256 µg/mL (Study 9603173) (2.4 Nonclinical Overview). M2 administration did not cause an increase in micronuclei in bone marrow, nor did it increase comet morphology in liver in an *in vivo* genotoxicity Study 9800811.

In a 4-week repeat-dose toxicity study (Study 1020-7461) with M2, microscopic changes considered related to the administration of M2 were observed in the seminal vesicles and prostate glands of male rats. Minimal to moderate acinar atrophy and decreased secretion were noted microscopically in the seminal vesicles and prostate glands of males that received ≥50 mg/kg/day, with a dose- related increase in the incidence and/or severity. These findings

correlated with small seminal vesicles and small prostate glands noted grossly in several male animals that received ≥100 mg/kg/day of M2 metabolite, as well as decreased prostate weights in animals that received ≥25 mg/kg/day of M2. Similar preliminary findings were observed in a 13-week rat toxicity study of M2 (Study 1020 7471) which is expected to report in the May 2023. In this study, macroscopic changes related to the administration of M2 were observed in the prostate gland of males dosed at ≥50 mg/kg/day, and in the seminal vesicles of males dosed at 100 mg/kg/day with M2, at the end of the main scheduled euthanasia. Microscopic changes considered related to the administration of M2 metabolite were also noted in the male sex accessory glands, in particular there was a dose-dependent, minimal to moderate decreased secretion in the prostate gland of males dosed at ≥50 mg/kg/day, minimal to mild acinar atrophy in the seminal vesicles of males dosed at 100 mg/kg/day and minimal to mild decreased secretion in the seminal vesicles of males dosed at ≥50 mg/kg/day with M2.

Findings observed in Study 1020-7461 (acinar atrophy, decreased secretion in the prostate gland and seminal vesicle glands, and the corresponding decreased prostate gland weight) occurred at levels slightly above clinical exposure levels; the clinical relevance of these findings remains unknown.

A 6-month toxicity study with M2 in rats is ongoing. A 6-month carcinogenicity study in transgenic mice with GNX was initiated in 2023 (final report submission planned for Q1 2025), and a 6-month carcinogenicity study in transgenic mice with M2 is planned to start in Q4 2025 to further address the long-term safety of GNX and the impact of its metabolite M2. Formal Weight-of-Evidence (WoE) assessments to evaluate the need for 2-year carcinogenicity studies in rats with GNX and M2 are planned for submission in Q4 2024. In addition, the need for a juvenile toxicity study with M2 will be evaluated in a WoE assessment planned for Q4 2024. An embryo-foetal development study with M2 in rats is planned to start in the Q1 2024. These studies are additional pharmacovigilance activities and post-authorisation measures (see Part III.2).

The human metabolite, M2, is not thought to present a safety concern in humans. The compound is a close analogue of an endogenous steroid (allopregnanolone) that is found in high levels in human plasma and the safety of GNX has been thoroughly evaluated in >1900 human subjects with no safety issues (and with presumably high M2 levels).

M43=M17 Metabolite

The characterisation of metabolite M43=M17 is not complete and in view of the potential long half-life of this metabolite, the long-term safety of this metabolite is currently unknown. Studies are planned with M17 to investigate in vitro drug-drug interactions (DDI) and in vivo pharmacokinetics (PK) with brain penetrance (see Part III.2).

Part II: Module SIII - Clinical trial exposure

As of 24 February 2021, 1,837 subjects across 42 completed clinical studies have received at least 1 dose of oral GNX, with another 77 subjects exposed to IV GNX and 16 subjects administered both oral and IV GNX. Study conduct was completed for 16 Phase 1 single-dose studies and 7 Phase 1 multiple-dose studies in healthy subjects (n=417). Patient studies include one Phase 1 study in adult migraine, and 18 Phase 2 or 3 studies in adult (partial onset seizures, migraine, postpartum depression, and post-traumatic stress disorder) and paediatric indications (infantile spasms, CDD [double-blind portion only] fragile X, protocadherin 19 (PCDH19) [double-blind portion only]). In these studies, oral doses ranged from 50 to 2000 mg/day using oral suspension, oral tablet, and oral capsule formulations. Overall, the to-be-marketed oral suspension formulation and dose was utilised in 8 Phase 2/3 studies with 381 patients exposed to GNX. Of these, 240 were paediatric patients and 141 were adults.

A summary of the overall patient safety database for all GNX formulations is presented in Table 2.

Table 2: Treatment exposure in the GNX clinical development programme

Patients exposed to treatment in the clinical development programme (N=2259)		
Clinical Trial Groups	**GNX (n=1513)**	**Placebo (n=746)**
Controlled trials conducted for CDD indication[a]	95	51
All other trials conducted for CDD indication	7	0
Controlled trials conducted for other indications[b]	1138	695
All other trials conducted for other indications	273	0

CDD=CDKL5 deficiency disorder; GNX=ganaxolone.
a: To be used in product's labelling.
b: For crossover trials, each subject was counted once for the treatment received in the respective period.
Source: 2.7.4 Summary of Clinical Safety, Table 2

The cumulative exposure of GNX in subjects, regardless of indication, from studies where datasets are available (N=1135) is presented by duration of exposure in Table 3. Total person time of exposure is 568.5 years.

Table 3: Cumulative exposure of GNX across all indications

Cumulative for all indications (All GNX Subjects, N=1135)		
Duration of exposure	**Patients, n (%)**	**Person time (years)**
0-1 Month	284 (25.0)	8.8
>1-3 Months	265 (23.3)	36.4
>3-6 Months	137 (12.1)	47.9
>6-12 Months	225 (19.8)	165.1
>12 Months	224 (19.7)	310.3
Total	**1135 (100)**	**568.5**

Notes: Exposure duration is calculated as date of last dose - date of first dose + 1.
The "All GNX Subjects" includes subjects from those studies with datasets available: 1042-0405, 1042-C14GNX-lac-1001, 1042-GNX.AME-1001, 1042-HAP-1001, 1042-DDI-1001, 1042-0900, 1042-PPD-2002, 1042-PPD-2003, 1042-0600, 1042-0601, 1042-0700, 1042-SE-2001, 1042-0500, 1042-0501, 1042-0800, 1042-0603, 1042-0604 and 1042-CDD-3001.
GNX=ganaxolone.
Source: RMP-specific TLF, table SIII.1.B

The evaluation of the safety of GNX oral suspension for the adjunctive treatment of seizures associated with CDD in patients 2 years of age and older is based primarily on the cumulative safety data available from one pivotal Phase 3 study and one supportive Phase 2a study in which a total of 102 subjects with CDD received GNX for a mean duration of exposure 351.4 days at doses up to the recommended therapeutic dose of 1800 mg/day for subjects weighing >28 kg and up to 63 mg/kg/day for subjects weighing ≤28 kg.

A single data pool, the 'All GNX CDD Population', consists of CDD subjects included in the safety populations who had at least 1 dose of the study drug in the following studies (data cut-off 24 Feb 2021):

- **Study 1042-CDD-3001**

  A double-blind, randomised, placebo-controlled trial of adjunctive GNX treatment in children and young adults with CDD followed by long-term OL treatment

  Of 101 subjects randomised in Study 1042-CDD-3001, 95 (94.1 %) completed the 17-week double-blind phase; 6 (5.9%) subjects discontinued from the study. The percentage of subjects who completed the double-blind phase was slightly higher in the GNX group (48/51 [96.0%]) than in the placebo group (47/50 [92.2%]). Overall, a total of 88 subjects (43 GNX and 45 placebo) continued in the open-label phase.

- **Study 1042-0900**

  Open label, proof-of-concept study of GNX in children with PCDH19 female paediatric epilepsy and other rare genetic epilepsies

  Seven (7) subjects were enrolled in the CDD cohort of which 4 (57.1%) subjects completed the 26-week open-label phase of the study; all 4 subjects entered and completed the 52-week open-label extension phase. Subjects who completed the 52-week open-label extension and continued to show a clinical response were permitted to continue GNX dosing; 1 subject was ongoing at the 24 Feb 2021 cut-off.

The All GNX CDD Population (n=102) is composed of 50 subjects from Study 1042-CDD-3001 who received GNX during the double-blind phase (of which 43 continued into the open-label

phase), 45 subjects from Study 1042-CDD-3001 who first received placebo during the double-blind phase and then went on to receive GNX during the open-label phase, and 7 CDD subjects from Study 1042-0900. The extent of exposure of subjects in the All GNX CDD Population is shown in Table 4. The mean duration of exposure was 351.4 days (minimum 14 days, maximum 1337 days, median 358.5 days). Modal dose for most subjects was the target dose of 1800 mg/day for subjects >28 kg or 63 mg/kg/day for subjects ≤28 kg (see Table 5).

Table 4: Exposure of GNX in CDD indication (All GNX CDD Population)

CDD Subjects (All GNX CDD Population)		
Duration of exposure	**Patients (%)**	**Person time (years)**
0-1 Month	3 (2.9)	0.1
>1-3 Months	7 (6.9)	1.0
>3-6 Months	10 (9.8)	3.9
>6-12 Months	32 (31.4)	23.7
>12 Months	50 (49.0)	69.5
Total	**102 (100)**	**98.1**

Notes: Exposure duration is calculated as date of last dose - date of first dose + 1.
The "All GNX CDD Population" consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
CDD=CDKL5 deficiency disorder; GNX=ganaxolone.
Source: RMP-specific TLF, table SIII.1.A

The exposure of patients to different doses of GNX across all indications (All GNX Subjects, N=1135) and specifically in the CDD indication (All GNX CDD Population, n=102) are presented below (Table 5). Exposure data are also presented by age and gender (Table 6) and by ethnic origin (Table 7).

Table 5: Exposure of GNX by dose

All GNX Subjects		
Dose of exposure	**Patients, n (%)**	**Person time (years)**
≤100 mg	29 (2.6)	0.1
>100 to ≤500 mg	97 (8.5)	21.5
>500 to ≤1000 mg	109 (9.6)	23.1
>1000 to ≤1800 mg	847 (74.6)	521.9
>1800 mg	53 (4.7)	2.0
Total (All doses combined)	**1135 (100)**	**568.5**
CDD Subjects (All GNX CDD Population)		
Dose of exposure	**Patients (%)**	**Person time (years)**
Subjects >28 kg (30 kg)[a]: <1800 mg/day	8 (7.8)	10.2
Subjects >28 kg (30 kg)[a]: 1800 mg/day	14 (13.7)	16.7
Subjects ≤28 kg (30 kg)[a]: <63 mg/kg/day	18 (17.6)	12.7
Subjects ≤28 kg (30 kg)[a]: 63 mg/kg/day	62 (60.8)	58.4
Total (All doses combined)	**102 (100)**	**98.0**

The "All GNX Subjects" includes subjects from those studies with datasets available: 1042-0405, 1042-C14GNX-lac-1001, 1042-GNX.AME-1001, 1042-HAP-1001, 1042-DDI-1001, 1042-0900, 1042-PPD-2002, 1042-PPD-2003, 1042-0600, 1042-0601, 1042-0700, 1042-SE-2001, 1042-0500, 1042-0501, 1042-0800, 1042-0603, 1042-0604 and 1042-CDD-3001.
The "All GNX CDD Population" consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
a: Subjects who were over 30 kg in study 1042-0900 and those who were over 28 kg in study 1042-CDD-3001 were titrated toward a target dose of 1800 mg/day. Subjects less or equal to these weight thresholds were titrated toward a target dose of 63 mg/kg/day.
CDD=CDKL5 deficiency disorder; GNX=ganaxolone.
Source: RMP-specific TLF, tables SIII.3.A, SIII.3.B

Table 6: Exposure of GNX by age group and gender

All GNX Subjects				
Age group	**Male**		**Female**	
	Patients, n (%)	**Person time (years)**	**Patients, n (%)**	**Person time (years)**
Infants (0 to 1 year)	23 (2.0)	12.7	32 (2.8)	25.5
Children (2 to 11 years)	53 (4.7)	20.8	86 (7.6)	73.0
Adolescents (12 to 17 years)	22 (1.9)	5.4	22 (1.9)	18.9
Adults (>18 years)	385 (33.9)	162.7	512 (45.1)	249.4
Total	**483 (42.6)**	**201 6**	**652 (57.4)**	**366.9**
CDD Subjects (All GNX CDD Population)				
Age group	**Male**		**Female**	
	Patients, n (%)	**Person time (years)**	**Patients, n (%)**	**Person time (years)**
Infants (0 to 1 year)	0	0	0	0
Children (2 to 11 years)	16 (15.7)	14.6	67 (65.7)	63.7
Adolescents (12 to 17 years)	4 (3.9)	2.8	13 (12.7)	14.7
Adults (>18 years)	0	0	2 (2.0)	2.3
Total	**20 (19.6)**	**17.4**	**82 (80.4)**	**80.8**

The “All GNX Subjects” includes subjects from those studies with datasets available: 1042-0405, 1042-C14GNX-lac-1001, 1042-GNX.AME-1001, 1042-HAP-1001, 1042-DDI-1001, 1042-0900, 1042-PPD-2002, 1042-PPD-2003, 1042-0600, 1042-0601, 1042-0700, 1042-SE-2001, 1042-0500, 1042-0501, 1042-0800, 1042-0603, 1042-0604 and 1042-CDD-3001.
The “All GNX CDD Population” consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
CDD=CDKL5 deficiency disorder; GNX=ganaxolone.
Source: RMP-specific TLF, tables SIII.2.A, SIII.2.B

Table 7: Exposure of GNX by ethnic origin (All GNX CDD Population)

CDD Subjects (All GNX CDD Population)		
Ethnic origin	**Patients, n (%)**	**Person time (years)**
Hispanic or Latino	10 (9.8)	6.0
Not-Hispanic or Latino	88 (86.3)	88.6
Unknown	2 (2.0)	1.7
Not reported	2 (2.0)	1.9
Total	**102 (100)**	**98.2**

The "All GNX CDD Population" consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
CDD=CDKL5 deficiency disorder; GNX=ganaxolone.
Source: RMP-specific TLF, table SIII.4.A

The majority of patients were White (94 [92.2%]), with the remaining 8 (7.8%) patients being of other race (which included 5 [4.9%] Asian patients); there were no patients of Black race.

Cumulative duration of exposure data to GNX in the subjects who received GNX in both the double blind and the OLE phases of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900 through 30 June 2022 is presented in Table 8.

Table 8: Duration of Exposure to Study Treatment (All Treated CDD Subjects)

	Placebo DB (N=51)	All Ganaxolone CDD (N=102)
Exposure duration categories, n (%)		
Any exposure	51 (100)	102 (100)
< 1 month	2 (3.9)	3 (2.9)
≥ 1 month	49 (96.1)	99 (97.1)
≥ 2 months	48 (94.1)	94 (92.2)
≥ 3 months	47 (92.2)	92 (90.2)
≥ 4 months	17 (33.3)	91 (89.2)
≥ 5 months	1 (2.0)	84 (82.4)
≥ 6 months	1 (2.0)	82 (80.4)
≥ 9 months	0	74 (72.5)
≥ 12 months	0	67 (65.7)
≥ 15 months	0	57 (55.9)
≥ 18 months	0	56 (54.9)
≥ 21 months	0	50 (49.0)
≥ 24 months	0	46 (45.1)
≥ 27 months	0	35 (34.3)
≥ 30 months	0	18 (17.6)
≥ 33 months	0	12 (11.8)
≥ 36 months	0	6 (5.9)
≥ 39 months	0	2 (2.0)
≥ 42 months	0	1 (1.0)

	Placebo DB (N=51)	All Ganaxolone CDD (N=102)
Exposure duration (days)		
n	51	102
Mean	113.9	573.3
SD	27.27	358.84
Min	2	14
Median	119.0	584.5
Max	189	1337
Sum	5807	58481
Subjects > 28 kg (30 kg): Modal dose (dose of longest exposure), n (%)		
< 1800 mg/day	1 (2.0)	8 (7.8)
1800 mg/day	10 (19.6)	14 (13.7)
Subjects <= 28 kg (30 kg): Modal dose (dose of longest exposure), n (%)		
< 63 mg/kg/day	6 (11.8)	17 (16.7)
63 mg/kg/day	34 (66.7)	63 (61.8)

- Abbreviation: CDD = CDKL5 Deficiency Disorder.
- Exposure duration is calculated as date of last dose/cutoff date whichever is earlier – date of first dose + 1.

The "Placebo DB" group consists of subjects treated with placebo during double-blind phase of study 1042-3001.
The "All Ganaxolone CDD" group consists of all subjects exposed to ganaxolone in any phase of study 1042-3001 and the CDD subset of subjects from study 1042-0900.
Source: Table 14.1.6.A Data Cut off 30 JUN 2022

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria from Study 1042-CDD-3001 are detailed below:

Exclusion criteria whose purpose is to ensure standardisation of the trial population that are common to most clinical trials are not discussed in this section, including:

- Previous exposure to GNX (i.e., the medicinal product under investigation)
- Exposure to any other investigational drug within 30 days or less than 5 half-lives prior to screening.
- Known sensitivity or allergy to any component in the investigational medicinal product, progesterone, or other related steroid compounds.

Exclusion criteria related to ongoing or recent conditions or treatments that may interfere with the study results and impact the safety and efficacy assessment of GNX are similarly not discussed, including:

- Concurrent use of ACTH, prednisone or other glucocorticoid was not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. Moderate or strong inducer or inhibitor anti-epileptic drugs were allowed (e.g., carbamazepine, phenytoin, etc.)
- Subjects on ACTH, prednisone or other systemically (non-inhaled) administered steroids were to be off the product greater than 28 days prior to screening.
- Subjects with a positive result on tetrahydrocannabinol (THC) or cannabidiol (CBD) test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit without prescription for Epidyolex in epilepsy were excluded from the study. Concomitant Epidyolex (CBD) use was allowed in the double-blind phase provided the subject had been on a stable dose for at least 1 month prior to screening and was expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD were allowed in the open-label phase.
- Use of dietary supplements or herbal preparations were not permitted if subject had been using them consistently for less than 3 months prior to screening or did not plan to remain on stable doses for the duration of the double-blind phase. Use of St. John’s Wort was not permitted.
- Changes in anti-epileptic drugs within the last month prior to screening: All AEDs must have been stable in dose for at least 1-month prior to screening unless otherwise noted.
- Any disease or condition (medical or surgical; other than CDKL5) at screening that might have compromised the haematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might have interfered with absorption, distribution, metabolism, or excretion of the investigational product, or would have placed the subject at increased risk.

Exclusion criteria identified for discussion are presented below:

West Syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of Infantile Spasms (IS) type; if EEG pattern/seizure type is uncertain, study inclusion should be reviewed and determined by the sponsor/sponsor delegate.

Reason for exclusion: West syndrome is a constellation of symptoms characterised by epileptic/infantile spasms, abnormal brain wave patterns called hypsarrhythmia and sometimes intellectual disability (NORD 2020). Any disorder that can lead to brain damage can be an underlying cause of West syndrome including a mutation in the *CDKL5* gene. Patients with known West syndrome were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of GNX in the genetically defined CDD patient population.

Is it considered to be included as missing information? No

Rationale: GNX is indicated for the adjunctive treatment of epileptic seizures associated with CDD in patients 2 years of age and older, as specified in the ZTALMY SmPC. Patients with West syndrome will not be treated unless identified as having a mutation in the *CDKL5* gene and hence diagnosed with CDD.

Active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (MRI).

Reason for exclusion: CDD is a complex epileptic encephalopathy. The translational product of the *CDKL5* gene is a protein of the serine-threonine kinase family. Changes in the level of CDKL5 protein suggest an important role in the process of neuronal formation and maturation. Although the exact molecular role of the protein has not been precisely defined, it is currently known that it is involved in proliferation, neuronal migration, neuronal formation, and neuronal growth, as well as in the development and functioning of synapses in brain maturation. Severe forms of epileptic encephalopathy include attacks not responsive to drug therapy, microcephaly, profound mental and psychomotor retardation, generalised hypotonia, and cortical vision disorders (Jakimiec 2020). Despite abnormal neuroimages being observed under MRI of CDD patients the changes are not very specific and are mostly related to (frontal) brain atrophy and white matter enhancement, mainly involving temporal lobes. Such abnormalities occur in many other neurological conditions and diseases and, therefore, cannot be used as the basis for diagnosis, differentiation, or prognosis of CDD. Patients with active CNS infection, demyelinating disease, degenerative neurological disease, or progressive CNS disease were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of GNX.

Is it considered to be included as missing information? No

Rationale: In clinical practice, patients with active CNS infection, demyelinating disease, degenerative neurological disease, or progressive CNS disease are not indicated for treatment with GNX. Adjunctive treatment of patients with epileptic seizures associated with CDD is the proposed indication for ZTALMY.

Unwillingness to withhold grapefruit, Seville oranges or star fruit from diet during the entire clinical trial.

Reason for exclusion: GNX is metabolised by CYP3A4 and CYP3A5. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent.

Studies have shown that grapefruit juice, Seville orange juice and star fruit juice inhibit CYP3A isozymes.

Is it considered to be included as missing information? No

Rationale: Inhibition of CYP3A4 has been shown to have mild to no effect on the exposure to GNX (Study 1042-DDI-1001). Following coadministration of GNX with itraconazole, a strong CYP3A4 and P-gp inhibitor, the $AUC_{0\text{-}inf}$ of GNX was increased by 17% and C_{max} was relatively unchanged (2.5 Clinical Overview, Section 3.2.4.2). In Study 1042-0115, results showed that grapefruit juice increases GNX C_{max} and AUC by 2- and 2.6-fold, respectively in the fasted state; however, the increased exposure did not reach the plasma concentration for GNX achieved in the fed condition, which was 4.2-fold for C_{max} and 2.8-fold for AUC (2.5 Clinical Overview, Section 3.2.4.2). However, since itraconazole has only a small effect on the PK of GNX and grapefruit/Seville orange/starfruit juices are weaker inhibitors, affecting primarily only intestinal enzymes (versus intestinal and hepatic enzymes for itraconazole), these fruits are no longer expected to have an effect on the PK of GNX.

Patients treated with CYP3A4/5 inhibitors can be monitored and any adverse reactions experienced by patients in clinical practice will be managed by guidance in the ZTALMY SmPC whereby ZTALMY should be titrated gradually to achieve the recommended daily dose. Physicians experienced in treating patients who are on concomitant medicinal products should evaluate the need for dose adjustments of ZTALMY or of the concomitant medicinal product(s) to manage potential drug interactions.

Unwillingness to withhold alcohol throughout the entire clinical trial.

Reason for exclusion: GNX can cause somnolence and sedation. These adverse reactions appear early in treatment and are dose-related; symptoms may decrease with continued treatment. Alcohol is a CNS depressant and could potentiate the somnolence and sedation effect.

Is it considered to be included as missing information? No

Rationale: In animal models, GNX has been shown to potentiate the effects of alcohol in a similar manner to that of benzodiazepines and valproic acid. Concomitant use of ZTALMY with CNS depressants (including alcohol) may increase the risk of sedation and somnolence. However, no reports of adverse effects with GNX and alcohol in adult epileptic subjects have been reported. The ZTALMY SmPC specifies that patients should be prohibited from drinking alcohol during treatment with ZTALMY.

Active suicidal plan/intent or active suicidal thoughts in the past 6 months or a suicide attempt in the past 3 years.

Reason for exclusion: As specified in the ZTALMY SmPC, AEDs have a class warning regarding an increased risk of suicidality and patients with epilepsy are known to have an elevated risk for suicide as compared to population controls. Suicidal behaviour and ideation have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials with AEDs has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known. Patients with known suicidal tendencies were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of GNX and to reduce the risk of premature discontinuation from the study.

Is it considered to be included as missing information? No

Rationale: GNX acts by increasing seizure threshold and blocking seizure propagation and is classed as an AED. Clinical trial data do not support an increased risk of suicidality in subjects treated with GNX. The ZTALMY SmPC advises patient's caregivers to monitor for signs of suicidal behaviour and ideation, or self-harm behaviour during treatment with GNX and when changes in the treatment regimen become necessary. Caregivers should be advised to seek medical advice should any signs of suicidal behaviour and ideation, or self-harm emerge.

Pregnant or breastfeeding

Reason for exclusion: Animal studies are insufficient with respect to reproductive toxicity (Module SII). It is not known if GNX crosses the placenta. As specified in the ZTALMY SmPC, GNX and its metabolites are excreted in human milk. A milk excretion study conducted in five healthy adult lactating women treated with a 300 mg oral dose of GNX showed GNX concentrations in breast milk to be approximately 4-fold higher than in plasma. The calculated maximum relative infant dose for GNX is approximately 0.157 mg/kg/day based on an average milk intake of 150 mL/kg/day, which is less than 1% of the maternal dose, and approximately 0.24% the labelled paediatric dose of 63 mg/kg/day. The effect of GNX on breastfed newborns/infants is unknown. As a precautionary measure, pregnant or breastfeeding patients were excluded from the clinical development programme, as is the case for the majority of investigative clinical trials.

Is it considered to be included as missing information? Yes

Plasma allopregnanolone sulphate (Allo-S) levels ≥ 6.0 ng/mL at the screening visit.

Reason for exclusion: Plasma allopregnanolone-sulphate (Allo-S) was hypothesized to be a predictive biomarker of the anti-epileptic treatment effect of GNX in patients with PCDH19-related epilepsy, which is caused by an inherited mutation of the *PCDH19* gene located on the X chromosome. This gene encodes for a calcium-dependent cell-cell adhesion molecule (PCDH19) that is expressed in the CNS and which appears to be involved in synaptic transmission and formation of synaptic connections during brain development (Depienne 2009). An anticonvulsant treatment effect signal of GNX in PCDH19-related epilepsy has emerged from an ongoing open-label flexible-dose exploratory study (Study 1042-0900) of GNX in children (age range 2-15 years) with rare genetic epilepsies with uncontrolled seizures despite multiple AED regimens (ClinicalTrials.gov Identifier: NCT02358538). In a PCDH19 patient cohort, distinctly different Allo-S levels were observed between responders, defined as a ≥25% decrease in seizure rate, and non-responders. Responders and non-responders had mean (± SD) plasma Allo-S concentrations of 501 ±430 pg/mL and 9,829 ±6,638 pg/mL, respectively. Subjects with high Allo-S are considered less likely to respond to GNX treatment. Patients with Allo-S levels ≥6.0 ng/ml at the screening visit were excluded from the Phase 3 study to avoid confounding factors that might impact the assessment of the efficacy of GNX in patients with CDD-related epilepsy.

Is it considered to be included as missing information? No

Rationale: Preliminary analysis of a subsequent placebo-controlled study in PCDH19-related epilepsy (Study 1042-PCDH19-3002) did not demonstrate a treatment response based on the putative biomarker, Allo-S. Similarly, the Phase 3 CDD study (1042-CDD-3001) has demonstrated that Allo-S levels do not predict treatment response and failed to support the original hypothesis. Patients with epileptic seizures associated with CDD will not be assessed for Allo-S levels prior to treatment with GNX. All patients to be treated will have ZTALMY titrated gradually over 4 weeks to allow for assessment of clinical response and tolerability in the process of attaining the recommended daily dose.

Aspartate transaminase (AST) or alanine transaminase (ALT) greater than 3 times the upper limit of normal (ULN) at study entry. If AST or ALT increases >3 times ULN during the study, subject should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Subject will be discontinued if levels do not decline to under 3 x ULN.

Total bilirubin levels greater than ULN at study entry. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin greater than ULN, the medical monitor can determine if a protocol exception can be made. If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.

Reason for exclusion: The influence of hepatic impairment on the PK of GNX had not been studied prior to the start of Study 1042-CDD-3001. As GNX is thought to be primarily cleared through hepatic metabolism, hepatic impairment would be expected to influence the PK of GNX and to increase exposure to GNX. Therefore, patients with mild, moderate, or severe hepatic impairment were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of GNX.

Is it considered to be included as missing information? No

Rationale:

The influence of hepatic impairment on the PK of GNX was investigated in a Phase 1, open-label hepatic impairment study (Study 1042 IHF-1001). The clinical study report (CSR) was completed on the 09 December 2022. No clinically significant effects on the exposures of GNX were observed following administration of a single oral dose of 300 mg in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Patients with severe (Child-Pugh C) hepatic impairment had an approximately 5.8-fold increase in $AUC_{0\text{-}inf}$ compared to those with normal hepatic function. The SmPC informs that the initial target dose should be one-third the recommended target dose in patients with severe hepatic impairment (Child-Pugh C). Specific dose titration tables for patients with severe hepatic impairment are provided. Higher or lower doses of GNX may be considered in patients with severe hepatic impairment based on individual clinical response and tolerability. Dose adjustment is not required in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

Subjects with significant renal insufficiency, estimated glomerular filtration rate (eGFR) <30 mL/min (calculated using the Cockcroft-Gault formula or Paediatric GFR calculator or Bedside Schwartz), were excluded from study entry or discontinued if the criterion was met post baseline.

Reason for exclusion: GNX is excreted in both faeces and urine, with the majority excreted in the faeces. Patients with mild, moderate, or severe renal impairment were excluded from the study to avoid confounding factors that might impact the assessment of the efficacy and safety of GNX.

Is it considered to be included as missing information? No

Rationale: A Phase 1, open-label renal impairment study (Study 1042-IRF-1001) has completed. The study demonstrated that for both GNX and unbound GNX, the rate and extent of absorption for subjects with normal renal function were numerically only slightly greater than or similar to those with severe renal impairment suggesting no impact on exposure for renally impaired subjects. This is further corroborated by the low estimate of the slope (β) on the impact of eGFR and creatinine clearance observed, suggesting no correlation between renal impairment and eGFR and creatinine clearance following oral dose administration of GNX. Further, oral GNX at a dose of 300 mg was safe and well tolerated in this study with no observed relationship in reporting of

adverse events and GNX. There was 1 reported adverse event (back pain) in the severe renal impairment group that was mild in intensity and considered not related to the study drug. No subjects discontinued as a result of an adverse event or abnormal safety assessment finding. The ZTALMY SmPC advises that patients with mild, moderate, or severe renal impairment can be administered ZTALMY without dose adjustment.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

As of 24 February 2021, 102 unique subjects with CDD (All GNX CDD Population) have received treatment with GNX ranging in duration from 14 days to 1337 days (median duration 358.5 days), with doses ranging from 457 to 2057 mg/day. Adverse reactions with a frequency greater than 1 in 34 could be detected and quantified assuming the background incidence of the adverse event is zero.

Alternatively, considering the 1135 GNX-treated patients (All GNX Subjects) regardless of indication, from studies where datasets are available (see Module SIII), adverse reactions with a frequency greater than 1 in 378 could be quantified in a data set of this size.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 9: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breastfeeding women	
Patients with relevant comorbidities:	
• Patients with hepatic impairment	In the clinical development programme patients were included if they had adequate hepatic function at study entry (AST and ALT ≤3 x ULN; bilirubin ≤ULN). If AST or ALT increased >3 x ULN during the study, subject was followed with weekly laboratory repeat testing and continued in study if levels were trending down. Subject was discontinued if levels did not decline to <3 x ULN. Patients with stable Gilbert's Syndrome resulting in bilirubin levels >ULN could be included if the medical monitor considered a protocol exception could be made. If total bilirubin increased to ≥1.5 x ULN during study, the subject was discontinued. (Module SIV.1). All subjects in the GNX treatment group in Study 1042-CDD-3001 had adequate hepatic function. However, the CSR for a Phase 1 hepatic impairment study in subjects with mild, moderate, and severe impairment along with matched controls was completed on 09 Dec 2022 and dosage recommendations for patients with hepatic impairment are included in the SmPC (Module SIV.1).

Type of special population	Exposure
• Patients with renal impairment	In the clinical development programme patients were included if they had adequate renal function at study entry (estimated glomerular filtration rate [eGFR] ≥30 mL/min) (Module SIV.1). GNX is biotransformed primarily by hepatic metabolism and a significant increase in exposure is not expected in subjects with renal insufficiency. To further characterise the use of GNX in patients with renal impairment, a Phase 1 study of oral GNX in subjects with renal impairment compared with matched normal controls was initiated after the 24 Feb 2021 data cut-off for this RMP and has completed. The study demonstrated that for both GNX and unbound GNX, the rate and extent of absorption for subjects with normal renal function were numerically only slightly greater than or similar to those with severe renal impairment suggesting no impact on exposure for renally impaired subjects.
• Patients with cardiovascular impairment	Patients with any disease or condition at screening that might compromise the cardiovascular system; were excluded from participation (Module SIV.1). In the GNX clinical development programme no cardiovascular risk has been identified (Module SII).
• Immunocompromised patients	None of the exclusion criteria prohibited immunocompromised subjects.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme.
Population with relevant different ethnic origin	Study 1042-CDD-3001 (n=101) comprised subjects who were White (92%), Asian (5%) and Other (3%) and mainly Not Hispanic or Latino ethnicity (86%). Ten percent (10%) of subjects were Hispanic/Latino with 2% of unknown ethnicity and 2% not reported (2.7.4 Summary of Clinical Safety, Table 16) The baseline demographics of subjects treated with GNX in the clinical development programme by ethnicity are presented in Table 7 (Module SIII).
Subpopulations carrying relevant genetic polymorphisms	Not applicable. All recruited patients had molecular confirmation of a pathogenic/likely pathogenic *CDKL5* variant. The genetic test classification for subjects participating in Study 1042-CDD-3001 (n=101) consisted of 58% pathogenic, 31% likely pathogenic and 11% variants of uncertain significance (9% having a mutation of a *de novo* variant in the kinase domain) (CSR 1042-CDD-3001 Table 14.1.4)

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

GNX was granted approval in the United States in March 2022. GNX has not been approved in any country outside of the United States. The data lock point for this RMP (24 February 2021) is prior to both approval and launch of GNX in the United States; there are minimal available post-marketing exposure data to present.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

GNX is associated with CNS-effects and therefore adverse events associated with abuse (e.g., euphoric mood, somnolence, dizziness) have been reported with GNX treatment. No intentional overdose abuse or misuse of GNX has been reported to date.

A validated clinical study was performed to evaluate the abuse potential of single oral doses of GNX in healthy recreational CNS depressant users (1042-HAP-1001). GNX at doses of up to a supratherapeutic dose of 2000 mg showed significantly less abuse potential compared with lorazepam (6 mg). Subjective effects of GNX peaked between 1 to 3 hours post-dose, but were relatively transient, generally lasting approximately 6 hours post-dose compared with 12 hours post-dose with lorazepam 6 mg. Effects of GNX on cognitive or motor impairment were small, sporadic, and markedly lower than those of lorazepam.

Regarding absolute abuse potential, GNX 400 mg produced responses that showed similar abuse potential to placebo; however, GNX 800 and 2000 mg each produced responses that were not similar to those of placebo. GNX 400 mg was not significantly different from placebo on key secondary endpoints (Overall Drug Liking visual analogue scale (VAS) maximum effect (E_{max}) and Take Drug Again VAS E_{max}), but did show significantly greater positive, sedative, and other effects compared with placebo. GNX 800 and 2000 mg showed significantly greater effects compared with placebo on the key secondary endpoints, as well as measures of positive, sedative, and other drug effects. GNX was not associated with significant negative effects at any dose level (2.5 Clinical Overview, Section 3.5.3).

In Good Laboratory Practice (GLP) pharmacology studies that assessed drug abuse liability, the responses elicited with GNX are consistent with Schedule IV drugs (drugs characterised with a low potential for abuse and low risk of dependence, such as benzodiazepines). Recently, GNX was placed in Schedule V of the Controlled Substances Act (CSA) of the United States. Schedule V controlled substances have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics (Drug Enforcement Agency (DEA)).

Whilst the potential for abuse is considered minimal, the ZTALMY SmPC includes a warning that ZTALMY has potential for abuse. GNX shares an internal/subjective interoceptive cue with benzodiazepines and dose-dependently supported self-administration in a rodent model of reward, suggested GNX has reinforcing characteristics similar to benzodiazepines.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Somnolence and sedation

GNX is a methyl analogue of the endogenous neurosteroid allopregnanolone, a derivative of progesterone. It is a neuroactive steroid that allosterically positively modulates $GABA_A$ receptors (comprised of α and γ units) in the CNS at sites that are distinct from other allosteric $GABA_A$ receptor modulators, such as benzodiazepines (Campo-Soria 2006). GNX also modulates extrasynaptic $GABA_A$ receptors that are comprised of α and δ subunits (Belelli 2006; Belelli 2005). CNS-related effects are not unanticipated based on the mechanism of action of GNX and in this way GNX can exhibit anticonvulsant activity as well as sedative effects.

In Study 1042-CDD-3001 (double-blind phase) GNX caused somnolence and sedation in 36.0% and 6.0%, respectively, of patients treated with GNX, compared with 15.7% and 3.9%, respectively, of patients treated with placebo (Table 10). Adverse reactions of somnolence and sedation appear early in treatment and are dose-related, and symptoms may diminish with continued treatment. In the open-label phase of Study 1042-CDD-3001, where all subjects received GNX, TEAEs were similar to the double-blind phase with somnolence (21.6%) being the second most frequently observed. Somnolence was reported by a higher proportion of subjects in the double-blind placebo group compared with the double-blind GNX group (26.7% vs 16.3%) which is consistent with these events occurring early in treatment or reducing with long-term treatment (2.7.4 Summary of Clinical Safety, Section 2.1.2.1.2).

A cut-off of ≥2% of participants of the All GNX CDD Population was used to define the most frequent TEAEs. In the All GNX CDD Population (n=102), somnolence was the most frequently reported TEAE (30 [29.4%] GNX subjects vs 8 [15.7%] placebo; Table 10). TEAE PTs related to somnolence such as of sedation (4 [3.9%] subjects), hypersomnia (4 [3.9%] subjects), and lethargy (4 [3.9%] subjects) were also reported (vs 3.9%, 0%, and 3.9% for placebo subjects, respectively). (Table 10; 2.7.4 Summary of Clinical Safety Table 30).

Table 10: Somnolence-related treatment emergent adverse events (>2% in GNX-treated subjects) in CDD subjects

System Organ Class (SOC)/ Preferred Term (PT)	Placebo (double-blind) (N=51) n (%)	GNX (double-blind) (N=50) n (%)	All GNX CDD Population (N=102) n (%)
Nervous System Disorders	20 (39.2)	27 (54.0)	58 (56.9)
Somnolence	8 (15.7)	18 (36.0)	30 (29.4)
Hypersomnia	0	2 (4.0)	4 (3.9)
Lethargy	2 (3.9)	2 (4.0)	4 (3.9)
Sedation	2 (3.9)	3 (6.0)	4 (3.9)

Note: A subject with multiple adverse events within a SOC or PT is counted only once.
MedDRA Version 23.0 was used for reporting adverse events.
The "Placebo (double-blind)" group consists of subjects treated with placebo during double-blind phase of Study 1042-CDD-3001. The "GNX (double-blind)" group consists of subjects treated with GNX during double-blind phase of Study 1042-CDD-3001. The "All GNX CDD" group consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
CDD=cyclin-dependent kinase-like 5 deficiency disorder; GNX=ganaxolone; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class
Source: 2.7.4 Summary of Clinical Safety, Table 28, Table 30

When a more recent cut of the data (22 June 2021) was analysed the TEAE profile in the All GNX CDD population was consistent with that of the earlier data cutoff. (23 February 2021). The same TEAEs were the most common and remained in the same ranking of frequency.

The median treatment duration was 358.5 and 119.0 days, respectively, for GNX-treated subjects versus placebo group, a 3-fold difference in extent of exposure. In the All GNX CDD Population (N=102), following adjustment for duration of treatment exposure, TEAEs occurred at a lower rate of 6.66/year (95% CI 6.17, 7.19) versus 11.01/year (95% CI 9.49, 12.77) for the placebo group (N=51). Specifically, the rates for the CNS-related TEAEs of somnolence, lethargy and sedation were all lower in GNX-treated subjects than those observed in placebo treated subjects (N=51) (0.4 vs 0.5, 0.05 vs 0.13 and 0.04 vs 0.13, respectively). Hypersomnia occurred at a higher rate (0.04 vs 0), with no difference in rate for gait disturbance (0.06) and no events of dizziness reported in either GNX-treated or placebo groups (RMP TLFs, Table 6A).

Table 11: Treatment emergent adverse events adjusted by treatment exposure

System Organ Class (SOC)/ Preferred Term (PT)	Placebo (double-blind) (N=51) (Total duration = 15.9 patient-year) n (rate [CI])	All GNX CDD Population (N=102) (Total duration = 98.1 patient-year) n (rate [CI])
Number of TEAE cases	175 (11.01 [9.49, 12.77])	654 (6.66 [6.17, 7.19])
Nervous System Disorders		
Somnolence	8 (0.05 [0.25, 1.01])	39 (0.40 [0.29, 0.54])
Lethargy	2 (0.13 [0.03, 0.50])	5 (0.05, [0.02, 0.12])
Hypersomnia	0	4 (0.04 [0.02, 0.11])
Sedation	2 (0.13 [0.03, 0.50])	4 (0.04 [0.02, 0.11])

Note: TEAEs are defined as any adverse event that occurs or worsens between first dose of study drug and up to the end of the study period. Special attention will be needed for subjects who were assigned to placebo during double-blind phase, as their reference dates for TEAEs were different during the double-blind period and open-label period.
Within a SOC or PT, the number of TEAE cases is counted.
MedDRA Version 23.0 was used for reporting adverse events.
The "Placebo (double-blind)" group consists of subjects treated with placebo during double-blind phase of Study 1042-CDD-3001. The "All GNX CDD" group consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900.
CDD=CDKL5 deficiency disorder; CI=confidence interval (based on Poisson distribution assumption); GNX=ganaxolone; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment emergent adverse event.
Source: RMP TLFs, Table 6A

Most TEAEs reported in the All GNX CDD Population were mild or moderate in severity (24.5% and 46.1%, respectively). A total of 21 (20.6%) subjects in the All GNX CDD Population reported severe TEAEs (2.7.4 Summary of Clinical Safety, Section 2.1.4). Overall, 6 (5.9%) subjects reported serious drug-related TEAEs in the All GNX CDD Population with one case each for the TEAEs of somnolence, lethargy and gait disturbance (2.7.4 Summary of Clinical Safety, Section 2.1.6.2).

Specifically, in the double-blind phase of Study 1042-CDD-3001 the most frequent study drug related, according to the investigator, TEAE by PT was somnolence and was reported by higher proportions of subjects in the GNX group compared to placebo group (17 [34.0%] vs 3 [5.9%]) (Table 12).

The most frequently reported drug-related TEAE in the All GNX CDD Population was somnolence (27 [26.5%] subjects) and PTs related to somnolence such as sedation (4 [3.9%] subjects), hypersomnia (3 [2.9%] subjects), and lethargy (3 [2.9%] subjects) were also reported (Table 12). Most drug-related TEAEs reported in the All GNX CDD Population were mild or moderate in severity (21 [20.6%] and 33 [32.4%] subjects, respectively). Seven (6.9%) subjects reported severe drug-related TEAEs in the All GNX CDD Population, of which one was somnolence, and one was hypersomnia These TEAEs are consistent with GNX's CNS effects and were reported in previous studies with GNX (2.7.4 Summary of Clinical Safety, Section 2.1.4).

Table 12: Somnolence-related drug-related treatment emergent adverse events (>2% in GNX-treated subjects) in CDD subjects

System Organ Class (SOC)/ Preferred Term (PT)	Placebo (double-blind) (N=51) n (%)	GNX (double-blind) (N=50) n (%)	All GNX CDD Population (N=102) n (%)
Number of Subjects with at least 1 drug-related TEAE	22 (43.1)	35 (70.0)	61 (59.8)
Nervous System Disorders			
Somnolence	3 (5.9)	17 (34.0)	27 (26.5)
Hypersomnia	0	2 (4.0)	3 (2.9)
Lethargy	2 (3.9)	2 (4.0)	3 (2.9)
Sedation	2 (3.9)	3 (6.0)	4 (3.9)

Note: A subject with multiple adverse events within a SOC or PT is counted only once.
Study drug related TEAEs are TEAEs that have been judged by the investigator to be possibly, probably or definitely related to the study drug for Study 1042-0900, and to be related to the study drug for Study 1042-CDD-3001.
MedDRA Version 23.0 was used for reporting adverse events.
The "Placebo (double-blind)" group consists of subjects treated with placebo during double-blind phase of Study 1042-CDD-3001. The "GNX (double-blind)" group consists of subjects treated with GNX during double-blind phase of Study 1042-CDD-3001. The "All Ganaxolone CDD" group consists of all subjects exposed to GNX in any phase of Study 1042-CDD-3001 and the CDD subset of subjects from Study 1042-0900
CDD=cyclin-dependent kinase-like 5 deficiency disorder; GNX=ganaxolone.
MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: 2.7.4 Summary of Clinical Safety, Table 38, Table 40

The number of subjects with at least 1 treatment-emergent SAE was 26 (25.5%) in the All GNX CDD Population (vs 5 [9.8%] for placebo). Overall, six (5.9%) subjects reported drug-related treatment-emergent SAEs in the All GNX CDD Population of which one subject experienced moderate somnolence along with dysphagia and hypotonia (both moderate severity) (2.7.4 Summary of Clinical Safety, Section 2.1.6.2).

A total of 13 (12.7%) subjects in the All GNX CDD Population have discontinued study drug due to TEAEs. Somnolence was the second most common TEAE leading to discontinuation (3 [2.9%] subjects). Hypersomnia led to discontinuation of study drug in 1 (1.0%) subject, with no TEAEs of sedation, lethargy, or gait disturbance leading to treatment discontinuation being reported (2.7.4 Summary of Clinical Safety, Table 50).

Somnolence was the most frequent TEAE leading to dose reduction or temporary study drug discontinuation (8 [7.8%] subjects) in the All GNX CDD Population and PTs related to somnolence such as sedation and hypersomnia (1 [1.0%] subject each) were also reported. 2.7.4 Summary of Clinical Safety, Section 2.1.7.3).

Somnolence was numerically higher in non-Hispanic subjects, but the small number of Hispanic subjects makes interpretation difficult. In general, the small numbers of subjects ≥12 years old, male, other race, Hispanic, and >28 kg weight category dosing hinders detection of meaningful differences by these subgroups (2.7.4 Summary of Clinical Safety, Section 5.1.3).

In general, the CNS effects of somnolence and sedation were typically non-serious, mild to moderate in intensity, appeared early in treatment, were self-limiting, dose-related, and

reversible. The frequency, severity, and seriousness of these events were consistent with the previous GNX clinical experience, indicating that these events are not specific for the CDD population.

Sedative complications occur with any number of AEDs and neurologists are sufficiently familiar with the management of the sedative effects of AEDs to be able to manage these adverse reactions during clinical practice. Somnolence and sedation are not an important risk of GNX as these reactions can be managed in clinical practice through healthcare professional awareness of the precautions to take with AEDs and adhering to the guidance in the ZTALMY SmPC.

The ZTALMY SmPC advises physicians that, based on individual clinical response and tolerability, any patient not tolerating the next dose step can be maintained at the lower dose for additional days before advancing to the next dose. If the next dose is still not tolerated, patients can drop back to the previous lower dose. In addition, although the recommendation is to administer the total daily dosage in 3 equal doses throughout the day, if this is not tolerated by a patient, the dose can be adjusted to manage symptoms such as somnolence, provided that the total daily dose is administered.

Somnolence and sedation are included in the special warnings and precautions section of the ZTALMY SmPC, which also advises that other CNS depressants, including concomitantly used anti-seizure medicinal products, opioids, antidepressants, and alcohol, could potentiate the somnolence and sedation effect.

In addition, the ZTALMY SmPC specifies that ZTALMY has a moderate to major influence on the ability to drive and use machines because it may cause somnolence, sedation, and sedation-related adverse reactions, such as fatigue and ataxia, and other CNS-related events such as dizziness. Patients should be advised not to drive or use machines.

- Rash

Rash is a common side effect of several AEDs. In the GNX development programme rash adverse events were identified as warranting special attention to better characterise the safety profile of the study drug. Rash was considered an Adverse Event of Special Interest (AESI) (Protocol 1042-CDD-3001; IB 07 Dec 2020) due to the structural and pharmacologic similarity of GNX to endogenous allopregnanolone which is derived from progesterone, and which is associated with autoimmune dermatitis and rash. Even though GNX lacks classical steroid hormone effects, and the 3-ß substitution of a methyl group prevents back-transformation of GNX to steroid intermediates, its structural similarity to pregnanolone prompted monitoring of rash as an AESI (2.7.4 Summary of Clinical Safety, Section 1.1.2). Only 2 SAEs of rash have been reported in the GNX development programme; during the most recent DSUR reporting period (11 Oct 2019 to 10 Oct 2020) no subjects treated with either GNX or placebo reported SAEs of rash. Of the 2 reported SAEs to date, one of the events resolved after discontinuation of the study drug. The second SAE was reported in the ongoing trial 1042-0900 and the event was resolving as of 10 Oct 2020. There have been no cases of Stevens Johnson syndrome or other clinically important skin toxicities reported in the GNX clinical development programme. In the All GNX CDD Population (n=102) 7 (6.9%) subjects reported rash versus 4 (7.8%) subjects in the placebo group. In Study 1042-CDD-3001 (double-blind phase), rash was the most common treatment-emergent AESI by PT, reported in 3 subjects in the GNX group and 2 subjects in the placebo group (2.7.4 Summary of Clinical Safety, Section 2.1.7.2).

In the All GNX CDD Population (N=102), following adjustment for duration of treatment exposure, rash occurred at a lower rate of 0.08/year (95% CI 0.04, 0.16) versus 0.25/year (95% CI 0.09, 0.67) for the placebo group (N=51) (RMP TLFs, Table 6A).

Overall, the accumulated evidence suggests that the cases of treatment-emergent skin rashes reported do not differ from non-serious rashes that are relatively commonly encountered and there has not been evidence to date of significant autoimmune skin reactions to GNX. Given the paucity of evidence and the absence of a safety signal, there are insufficient grounds to retain rash as an AESI or as an important potential risk, nor does the evidence suggest a causal association between the administration of GNX and the occurrence of rash. Furthermore, there is no evidence that history of allergic reactions in the CDD population predisposed subjects to later skin reactions when taking GNX (2.7.4 Summary of Clinical Safety, Section 2.1.7.2).

- Drug interactions with CYP3A4/5 inhibitors and inducers

Drug-drug interactions with CYP3A4/5 inhibitors and inducers is not an important risk of GNX as these can be managed in clinical practice, through increased awareness of potential interactions and recommendations in the ZTALMY SmPC.

The changes in GNX exposures when coadministered with strong, moderate, or weak CYP3A4 inhibitors are not expected to be clinically significant. Coadministration of GNX with itraconazole, a strong CYP3A4 inhibitor, increased the GNX AUC by 17% in healthy subjects (the C_{max} was unchanged).

Concomitant use of rifampicin, a strong CYP3A4 inducer, decreased the $AUC_{0\text{-}inf}$ of GNX by approximately 57-68%. Enzyme inducing antiepileptics (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) and St. John's Wort may result in similarly lower plasma exposures of GNX. In patients on a stable dose of GNX or in patients initiating or increasing the dose of concomitant enzyme-inducing antiepileptic drugs or St. John's Wort, a dose increase may be necessary; however, the maximum daily dose must not be exceeded.

AEDs that are strong CYP3A4 inducers (e.g., carbamazepine and phenytoin) have been administered concomitantly with GNX in clinical studies.

- Ethanol interaction

In animal models, GNX has been shown to potentiate the effects of alcohol in a similar manner to that of benzodiazepines and valproic acid. Concomitant use of GNX with CNS depressants (including alcohol) may increase the risk of sedation and somnolence. Patients should not use alcohol during treatment with ZTALMY.

Known risks that do not impact the risk-benefit profile

- None

Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

There are no identified risks considered important for inclusion in the list of safety concerns for GNX.

Important Potential Risk 1: Long term safety (including sexual maturation and growth)

Risk-benefit impact:

In non-clinical studies, a delay in sexual maturation and growth were observed at exposure levels that were similar or lower to clinical exposure levels. The observed delay in sexual maturation did not result in any effects on reproductive capability as adults (Module SII). Available clinical data and the duration of exposure are limited (SVII.3.1.). Effects on sexual maturation and growth need to be followed up for a longer period considering that these potential adverse events will have a longer latency.

ZTALMY is subject to additional monitoring to allow quick identification of new safety information. Furthermore, additional pharmacovigilance activities are planned to further characterise the important potential risk of long term safety (including delay in sexual maturation and growth) (Part III.2).

The benefit of GNX as adjunctive treatment of epileptic seizures associated with CDD in patients who are often subject to frequent and debilitating daily seizures may outweigh the concern of long-term use of GNX. The risk to patients with long-term use of ZTALMY is currently not known.

Important Potential Risk 2: Suicidal behaviour and ideation

AEDs have a class warning about an increased risk of suicidality. Patients with epilepsy are at elevated risk for suicide as compared to population controls (Christensen 2007). In a comprehensive search of the entire GNX clinical development programme including completed and ongoing studies, a total of 9 reports of suicidality were identified in >1600 subjects exposed to GNX. In completed placebo-controlled studies, 1 (0.1%) TEAE of suicidality (PT Suicidal ideation) occurred in the GNX group (N=1101) while 3 TEAEs (0.4%; Suicidal ideation [2] and Suicide attempt [1]) occurred in the placebo group (N=743) (GNX IB, 03 Jun 2021, Table 56). Specifically, in subjects with epilepsy in completed placebo-controlled studies there were no TEAEs of suicidality in the GNX group (N=325) and 1 (0.4%) TEAE (Suicidal ideation) in the placebo group (N=274) (GNX IB, 03 Jun 2021, Table 59).

In the All GNX CDD Population (N=102), following adjustment for duration of treatment exposure, both suicidal ideation and suicide attempt had a zero rate per year; the placebo group (N=51) also had a zero rate for these TEAEs (RMP TLFs, Table 6A).

Suicidality has been reported in open-label GNX studies in 3 subjects with epilepsy and in 3 subjects with postpartum depression. For the 3 subjects with epilepsy, all were also receiving 1 to 3 AEDs at the time of the event; all 3 subjects with postpartum depression reported active suicidal ideations at 1 time point each and the subsequent visit results returned to baseline. In a Phase 3 trial (Study 1042-0603) of GNX in treatment refractory focal onset seizures, shifts to the category of any suicidal ideation or behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) during the study were very infrequent and were similar for both the GNX and placebo groups (GNX IB, 03 Jun 2021).

Risk-benefit impact:

The benefit of GNX as adjunctive treatment of epileptic seizures associated with CDD in patients who are often subject to frequent and debilitating daily seizures outweighs the important potential risk of suicidal behaviour and ideation that has yet to be confirmed in patients treated with GNX and can be managed in clinical practice through healthcare professional awareness of the precautions to take with AEDs and adhering to the guidance in the ZTALMY SmPC.

The ZTALMY SmPC informs healthcare professionals that suicidal behaviour and ideation have been reported in patients treated with AEDs in several indications. A meta-analysis of randomised placebo-controlled trials with AEDs has shown a small increased risk of suicidal behaviour and ideation. However, the mechanism of this risk is unknown, and the available data do not exclude the possibility of an increased risk with GNX.

Patient's caregivers are advised to monitor for signs of suicidal behaviour and ideation, or self-harm behaviour during treatment with GNX and when changes in the treatment regimen become necessary. Caregivers should be advised to seek medical advice should any signs of suicidal behaviour and ideation, or self-harm emerge.

Missing information 1: Use in pregnancy and during breastfeeding

There are limited data on use of GNX in pregnant women since pregnant or breastfeeding patients were excluded from the clinical development programme (Module SIV.1; Module SIV.3). Available pharmacokinetic data in animals have shown excretion of GNX and its metabolites in milk. A milk excretion study conducted in five healthy adult lactating women treated with a 300 mg oral dose of GNX showed GNX concentrations in breast milk to be approximately 4-fold higher than in plasma (Module SIV.1).

Risk-benefit impact:

The benefit of GNX as adjunctive treatment of epileptic seizures associated with CDD in patients who are often subject to frequent and debilitating daily seizures may outweigh the use of GNX in pregnancy and during breastfeeding based on an individual risk-benefit assessment conducted by the prescriber. The risk to pregnant women and mothers nursing an infant are currently not known.

The ZTALMY SmPC informs healthcare professionals that there are limited data on the use of GNX in pregnant women whilst animal studies are insufficient with respect to reproductive toxicity. ZTALMY is not recommended during pregnancy and in woman of childbearing potential not using contraception.

Furthermore, the ZTALMY SmPC specifies that GNX and its metabolites are excreted in human milk. However, since the effect of GNX on breastfed newborns/infants is unknown, healthcare professionals must decide whether the patient should discontinue breast-feeding or discontinue ZTALMY therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

There are no identified risks considered important for inclusion in the list of safety concerns for GNX.

Important Potential Risk 1: long term safety (including delayed sexual maturation and growth)

Potential mechanisms:

Ganaxolone has the same core structure as allopregnanolone, but with the addition of a 3β-methyl group to prevent enzymatic conversion to an entity (i.e., 3-keto) active at nuclear progesterone receptors. GNX is a neuroactive steroid that positively and allosterically modulates gamma-aminobutyric acid type A (GABAA) receptors in the central nervous system (CNS).

A study investigating circulating levels of allopregnanolone in children of different ages suggested that allopregnanolone may be involved in adaptive neuroendocrine mechanisms related to puberty (Fadalti 1999). However, a mechanism whereby GNX may cause a delay in sexual maturity and growth is not known.

Evidence source(s) and strength of evidence:

Decreased bodyweight gain and a significant delay in sexual maturation was observed in non-clinical studies. However, the observed delay in sexual maturation did not result in any effects on reproductive capability as adults. The human relevance of these findings is unknown at present as there are insufficient clinical safety data to assess adverse effects with a long latency or long term use effects.

Characterisation of the risk:

Clinical safety data generated to date from healthy volunteers, adult and paediatric patients show no significant toxicity for GNX and a lack of hormonal effects suggesting a lack of hormonal impact on bone density. There were no effects observed on steroidal reproductive hormones in rats and dogs following repeated dosing.

Non-clinically, there was a significant delay in sexual maturation. However, this this did not affect oestrous cyclicity or any fertility or reproductive parameters (Part II:Module SII).

In 2 juvenile animal studies a delay in sexual maturation was observed; however, there are inconsistencies between the 2 studies. In the first study (COY 2/950920) the observed delay in sexual maturation was attributed to a growth delay rather than a direct effect on sexual maturation. In the second study (00398515) the findings were not secondary to a growth delay and were therefore considered test article-related and adverse; however, the observed delay in sexual maturation did not result in any effects on reproductive capability in these animals as adults.

Regarding Tanner staging, in CDD patients participating in study 1042 CDD-3001, at screening, more than half of all subjects in each treatment group (71.4% in the GNX group, 65.0% in the placebo group) were Tanner Stage 1 (1042 CDD-3001 CSR Table 14.3.10). Overall, there were no medically important differences in baseline Tanner Stage between the GNX and placebo groups. At Week 52, there was an overall small numerical shift from lower Tanner stages to higher Tanner stages. This small shift was expected given that the majority subjects were at the pre-puberty age (mean and median age of 7.26 and 6.00 years old, respectively [see 1042-CDD-3001 CSR Table 5]). Furthermore, the same trend appeared in subjects regardless of if they had received placebo or GNX in the double-blind period of study 1042-CDD-3001.

Risk factors and risk groups:

General risk factors for a delay in sexual maturation include: chronic illnesses (sickle cell anaemia, inflammatory bowel disease, cystic fibrosis, celiac disease, etc); psychosocial

conditions (depression, anxiety, anorexia nervosa, excessive exercise), Genetic conditions (Kallman syndrome, brain mass or tumour, Klinefelter syndrome, testicular regression syndrome, autoimmune ovarian failure, Turner syndrome), radiation therapy, testicular surgery, surgery to ovaries (Tang 2022).

Preventability:

The SmPC informs of the delay in sexual maturation and growth observed in the non-clinical studies. ZTALMY is a prescription only medicine and is prescribed by physicians experienced in the treatment of epilepsy. No other specific risk minimisation measures are in place for this potential risk.

Impact on the risk-benefit balance of the product:

The benefit of GNX as adjunctive treatment of epileptic seizures associated with CDD in patients who are often subject to frequent and debilitating daily seizures may outweigh the concern of long-term use of GNX. However, the long-term risks of ZTALMY have not been established currently and additional pharmacovigilance activities are planned to further characterise the risks (Part III.2).

Public health impact:

There is insufficient clinical data to assess the public health impact of this potential risk.

Important Potential Risk 2: Suicidal behaviour and ideation

Potential mechanisms:

AEDs have a class warning about an increased risk of suicidality. Patients with epilepsy are at elevated risk for suicide as compared to population controls (Christensen 2007). The mechanism of this risk is unknown. The available data do not exclude the possibility of an increased risk with GNX.

Evidence source(s) and strength of evidence:

In a comprehensive search of the entire GNX clinical development programme including completed and ongoing studies, a total of 9 reports of suicidality were identified in >1600 subjects exposed to GNX. In completed placebo-controlled studies, 1 (0.1%) event of suicidality occurred in the GNX group while 3 events (0.3%) occurred in the placebo group.

Characterisation of the risk:

Specifically, in subjects with epilepsy in completed placebo-controlled studies there were no TEAEs of suicidality in the GNX group (N=325) and 1 (0.4%) TEAE (PT Suicidal ideation) in the placebo group (N=274) (GNX IB, 03 Jun 2021, Table 59).

Suicidality has been reported in open-label GNX studies in 3 subjects with epilepsy and in 3 subjects with postpartum depression. For the 3 subjects with epilepsy, all were also receiving 1 to 3 AEDs at the time of the event; all 3 subjects with postpartum depression reported active suicidal ideations at 1 time point each and the subsequent visit results returned to baseline. No suicidality has been reported in GNX studies conducted in healthy subjects. In a Phase 3 trial (Study 1042-0603) of GNX in treatment refractory focal onset seizures, shifts to the category of any suicidal ideation or behaviour assessed by the Columbia Suicide Severity Rating Scale (C-SSRS) during the study were very infrequent and comparable between GNX and placebo groups (GNX IB, 03 Jun 2021).

There were no events of suicidality reported in subjects in Study 1042-CDD-3001 nor in the All GNX CDD Population. Overall clinical trial data to date do not support an increased risk of suicidality in subjects treated with GNX. Patients treated with GNX should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Risk factors and risk groups:

According to the World Health Organisation (WHO 2021), more than 700,000 people die due to suicide every year in the general population, with suicide being the fourth leading cause of death in 15 to 19-year-olds. While suicide is relatively rare in children, in Europe, where youth suicide rates are tending to decrease, suicide is ranked as the second most frequent cause of death in those aged 10-19 years. In general, the presence of a mental disorder substantially increases suicide risk but moments of crisis with a breakdown in the ability to deal with life stresses (such as education, living situation, or peer pressure) can have a contributory role (Bilson 2018).

It is unknown if there is a background tendency towards suicidal behaviour and ideation in the specific CDD population.

Preventability:

In general key prevention strategies can be population based involving mental health promotion, education, awareness by campaigns on mental resilience, careful media coverage, and limited access to means of committing suicide. In addition, high-risk subgroups can be targeted for example by implementing specific school-based programmes, providing crisis hotlines and online help, and where possible detecting and coaching dysfunctional families (Bilson 2018).

The ZTALMY SmPC advises patient's caregivers to monitor for signs of suicidal behaviour and ideation, and self-harm behaviour during treatment with GNX and when changes in the treatment regimen become necessary. Caregivers are advised to seek medical advice should any signs of suicidal behaviour and ideation, or self-harm behaviour emerge.

Impact on the risk-benefit balance of the product:

Suicidality is an important potential risk although currently the clinical data do not support an increased risk of suicidality in subjects treated with GNX. CDD is a serious and potentially life-threatening condition with limited effective therapeutic options for treatment of the CDD associated epileptic seizures.

The benefit of GNX as adjunctive treatment of epileptic seizures associated with CDD outweighs the important potential risk of suicidal behaviour and ideation which can be appropriately managed in clinical practice through healthcare professional awareness of key aspects of the proposed labelling and adherence to the guidance in the ZTALMY SmPC that advises monitoring of patients for signs of suicidal behaviour and ideation, or self-harm behaviour.

The data do not impact the overall positive benefit-risk profile for GNX as adjunctive treatment for patients with CDD.

Public health impact:

Although AEDs have a class warning about an increased risk of suicidality, clinical data in subjects treated with GNX do not currently support a similar increased risk of suicidality and the impact on public health is expected to be low.

SVII.3.2. Presentation of the missing information

Missing information 1: Use in pregnancy and during breastfeeding

Evidence source:

Use of GNX during pregnancy and breastfeeding has not been evaluated in the clinical development programme and there are no data available for GNX exposure in pregnant women or during breastfeeding. Available pharmacokinetic data in animals have shown excretion of GNX and its metabolites in milk. A milk excretion study conducted in five healthy adult lactating women treated with a 300 mg oral dose of GNX showed GNX concentrations in breast milk to be approximately 4-fold higher than in plasma (Module SIV.1). Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at maximum tolerated doses that were below clinical exposures (Module SII). In the rat fertility and early embryonic development study, alterations in oestrous cyclicity occurred at the high dose level, however, there were no effects on spermatogenesis, reproductive performance, fertility, and early embryonic development. In the combined embryo-foetal development and pre- and postnatal development study in rats, there were no effects of GNX on embryo-foetal growth, survival, or morphology at the high dose level. In the postnatal phase of the study, gestation length was slightly lengthened and slight delays in offspring growth and related developmental milestones occurred at the high dose level of 40 mg/kg/day. There were no effects of GNX on postnatal survival, behavioural function, or reproductive capability at the high dose level of 40 mg/kg/day.

Use in pregnancy and during breastfeeding is an area of missing information.

Anticipated risk/consequence of the missing information:

Findings from studies in animals may be relevant for humans and in the absence of data in humans suggest minimal safety concern with use of GNX during pregnancy. Furthermore, ZTALMY is indicated for the adjunctive treatment of epileptic seizures associated with CDD in patients 2 years of age and older. Epileptic seizures are usually the first symptom of CDD commencing in 96.9% of patients in the first six months of life and in 90% in the first three months of life (Jakimiec 2020; Mangatt 2016), with most individuals who have been identified with CDD being under 18 years of age (Module SI).

Hence, with the majority use of ZTALMY anticipated in children and adolescents, use of ZTALMY during pregnancy or breastfeeding is anticipated to be very minimal. ZTALMY is not recommended during pregnancy and in woman of childbearing potential not using contraception. Furthermore, the SmPC advises healthcare professionals to decide whether a female patient should discontinue breast-feeding or discontinue ZTALMY therapy taking into account the benefit of ZTALMY therapy for the woman versus the benefit of breastfeeding for the infant.

Part II: Module SVIII - Summary of the safety concerns

Table 13: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Long term safety (including sexual maturation and growth) • Suicidal behaviour and ideation
Missing information	• Use in pregnancy and during breastfeeding

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific follow-up questionnaire for the missing information on pregnant and lactating women:

- A pregnancy follow-up questionnaire will collect specific data related to exposure during pregnancy and lactation in the post-marketing period (Annex 4).

Other forms of routine pharmacovigilance activities for the safety concerns:

- None

III.2 Additional pharmacovigilance activities

EURAP Observational Study Summary

Study short name and title:

EURAP Observational Study

An International Registry of Antiepileptic Drugs and Pregnancy

Rationale and study objectives:

The use of AEDs during pregnancy has been associated with an increased risk of birth defects. It is unclear if some AEDs are safer to use during pregnancy than others. There are limited data on use of GNX in pregnant women since pregnant or breastfeeding patients were excluded from the clinical development programme. The primary objective of participation in the EURAP observational study is to evaluate and determine the comparative degree of safety of GNX in pregnant women, with reference to and in combination with other antiepileptic drugs, including the evaluation of any specific pattern of major malformations, dose-effect relationships and other risk factors.

Participation in the EURAP observational study will help to provide meaningful conclusions with respect to the safety of GNX in pregnancy through an international collaboration generating large numbers of female patients of childbearing age.

Study design:

This is an observational study and does not interfere with the treatment prescribed by the patient's physician. The aim is to collect information concerning risk factors, exposures during pregnancy and pregnancy outcome. The data collected are part of the information that should be generally available during good medical care; the study does not entail any special evaluation procedure or extra visits.

All data collection is conducted using a standardised Case Record Form (CRF). Once enrolled women are followed up and information on progress of the gestation entered in the CRF at the end of each pregnancy trimester. Follow-up should continue until the infant reaches one year of age. Five sub-forms (A-E) of the CRF are available for completion at enrolment; after the first,

second, and third trimesters; within 3 months after delivery; and after proband has completed one year of age (no later than 14 months post-delivery).

Baseline demographic variables, risk factors and relevant clinical variables will be summarised descriptively to characterise the study population. For continuous data, statistical description will include arithmetic mean, standard deviation, and range, whilst categorical data will be tabulated by frequencies and percentages. Multiple logistic regression will be used to evaluate AED effects on the incidence of major malformations and intrauterine growth retardation, both as main effects and interactions when administered in polytherapy. In particular, multivariable analysis will focus on the assessment of the effects of individual AEDs and their combinations in relation to: 1) maternal age; 2) familiar history of teratogenic events; 3) exposure to other (non-AED) known teratogens; 4) smoker's status; 5) alcohol consumption; 6) other potential teratogens; 7) AED dosage (in absolute terms and in terms of defined daily dosages or their sums); 8) type of epilepsy (partial or generalised) and 9) frequency of convulsive seizures during the first trimester of pregnancy. All computations will be performed using SAS software procedures.

Study population:

All women taking AEDs at the time of conception are eligible for inclusion whether the indication for treatment is epilepsy or other disorders. To avoid selection bias, only pregnancies enrolled before foetal outcome is known and within week 16 of gestation contribute to the prospective study.

Milestones:

Update reports will be received half-yearly from the EURAP Central Project Committee, along with more detailed but anonymised information on pregnancy outcome after exposure specifically to GNX. Data received will be reviewed on an on-going basis as a part of signal detection and reported within PSURs, when available.

CANDID Study Summary

Study short name and title:

Study LLF001 (CANDID)

Endpoint Enabling Study in Cyclin-dependent kinase-like 5 Deficiency Disorder

Rationale and study objectives:

The objectives of this global study are to assess the clinical characteristics of CDD across multiple domains and to understand the longitudinal trajectories of CDD patients across the various clinical outcomes. The study will assess clinical outcomes related to seizures, sleep, behaviour, cognition, global development, and quality of life as well as regular safety assessments, including adverse events. Adverse events of particular interest are infection-related adverse events, aspiration pneumonia, gastrointestinal-related adverse events, and somnolence. As this is an exploratory observational study, no formal statistical hypothesis testing is planned, and data will be presented using descriptive statistics.

Study design:

This is a longitudinal, observational study which will prospectively follow individuals with confirmed CDD over the course of 3 years. It is formally sponsored by the Loulou Foundation with support from 7 distinct organisations including Marinus. Medical history and concomitant

medications will be collected during the baseline visit as well as during follow-up visits over the planned 3-year study. Medical history will include developmental history, seizure onset (age), seizure classification, clinically significant co-occurring conditions, and prior medical interventions. All past and present medications used within 4 weeks prior to baseline will also be collected as well as details of psychosocial and non-pharmacological interventions used over the past year. Demographic data collected will include age, sex, race/ethnicity, as well as participation in early intervention programs. A complete physical exam will be collected by the investigator. A paper diary will be provided to the parents/caregivers for their completion daily for the first year of the study. For the second- and third-year visits, the diary will be completed over a week on a monthly basis. Monitoring and recording of all adverse events and SAE will be performed up to the 12-month follow-up visit. After the 12-month visit, only adverse events related to study procedures (ie, fatigue) and SAEs will be recorded.

Enrolment will occur on a rolling basis in up to 40 centres. Planned countries include the US, Canada, UK, France, Spain, Italy, Germany, and Belgium. Study procedures will include in-clinic evaluations at baseline, 6, 12, 18, 24 and 36 months with remote assessments, using an abbreviated schedule of assessments, at 3, 9 and 30 months.

Study population:

The study aims to enrol up to 100 patients, males and females, with CDD between the ages of newborn and 55 years. Of these patients, it is anticipated that approximately 10 patients recruited will have taken GNX at some point given that GNX is now approved in the United States and is available in many countries, globally, via a compassionate use mechanism. It is recognised that this sample will not provide an adequate basis for confident conclusions regarding the long-term safety of GNX.

Milestones:

Milestone reports will be provided after at least 50 participants have completed baseline, after 50 participants have completed the first-year visit, and once approximately 100 participants have completed the first year. Annual study updates will be available to Marinus on or before the 31 January each year. Data received will be reviewed and reported within PSURs, when applicable to ganaxolone. Annual study updates (Data Lock Point [DLP]: 17 March) will be provided in parallel with the ganaxolone PSUR, (per ganaxolone PSUR reporting cycle dates stated in list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs_.xlsx (live.com)).

Orphan Disease Center CDKL5 Deficiency Disorder International Patient Registry

Study short name and title: CDKL5 Deficiency Disorder International Patient Registry

(ODC-IPR-CDD-01, NCT04486768)

Rationale and study objectives:

The primary objective of the registry is to collect and enable sharing of real-world demographic, clinical, patient reported outcome (PRO), and treatment data collected from patients with CDD or their legal guardians, and ultimately, their clinicians.

Secondarily, the CDKL5 Registry aims to aid in establishing best practices in standard of care for CDD, to inform clinical study design by collecting real-world data and providing access to the scientific and research community, to enable research through data sharing, to understand patient needs and quality of life factors, and to enable rapid recruitment by connecting patients to clinical trials.

Study design:

This non-interventional, observational, international, prospective, natural history registry will follow up to 500 patients diagnosed with CDD over several years through both the patients/caregivers and their clinicians. The reporting will be descriptive with no formal hypotheses to be tested. Initial data will be collected upon enrolment in the registry, followed by the collection of additional CDD-specific data on a bi-annual/ annual basis. No procedures will be performed as part of this registry. Clinician-entered data will be collected following standard of care visits conducted as part of patients' ongoing clinical care.

This registry contains several surveys that will be released for patient/caregiver completion at enrolment and at time points following enrolment. These surveys can be completed on any computer that is connected to the internet. The structure of the CDKL5 Registry allows for the addition of new questionnaires to the data collection effort and questions concerning sexual maturation and growth are to be included.

Study population:

Patients of any age with a diagnosis of CDD confirmed by a clinician or a genetic test.

Milestones:

Data received will be reviewed and reported within PSURs, when applicable to ganaxolone. Study updates will be provided every 6 months (DLPs:17 March and 17 September) in parallel with the ganaxolone PSUR (per ganaxolone PSUR reporting cycle dates stated in list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs_.xlsx (live.com)).

GNX Steady-State Metabolite Study

Study short name and title:

GNX Steady-State Metabolite Study

Rationale and study objectives:

To characterise the GNX metabolite pattern at steady state either through a re-analysis of samples retained from the 1042-TQT-1001 study (if feasible) or through the conduct of an additional Phase 1 study in healthy volunteers (if relevant).

Study design:

A re-analysis of retained samples from Study 1042-TQT-1001 will be performed if feasible.

If the re-analysis is not feasible, a PK study in healthy subjects receiving 600 mg GNX oral suspension three-times daily for 3 weeks will be conducted with PK assessments performed weekly. The PK profile of GNX, M2, and any other potential metabolites will be characterised.

Study population:

Healthy subjects (N=12) (if relevant)

Milestones:

Re-analysis of 1042-TQT-1001 study (if feasible)Q4 2023

PK study Q1 2025 (if relevant)

GNX Transgenic Mouse Carcinogenicity Study

Study short name and title:

GNX Transgenic Mouse Carcinogenicity Study

A 26-week Oral Gavage Carcinogenicity Study of Ganaxolone (GNX) in Hemizygous CByB6F1-Tg(HRAS)2Jic Mice

Rationale and study objectives:

In addition to the 6-month toxicity study in rats, a 6-month carcinogenicity study in mice is planned to further evaluate mortality and morbidity, terminal histopathology, and tumour statistics in order to address the safety concern of long-term use. Study results will help support the long-term safety of GNX in humans.

Study design:

Compliance: GLP

Pretreatment period: approximately 10 days

Dosing Regimen:

- GNX (twice daily [12 hours apart] for 182 days).
- Positive control (three times during Week 1)

Route of Administration: oral gavage (GNX); positive control dosed via IP injection

Mortality/Morbidity: Twice daily

Detailed observations: Weekly and at termination on all main animals

Cage-side Observations: Daily on all animals

Body Weight: Day 4, weekly, and at termination on all animals

Clinical Pathology Parameters: A blood sample will be collected at termination from all animals and a blood smear will be prepared. Slide review will only by performed if necessary.

Toxicokinetic sample collection will be conducted on Days 1 and 180 (relative to the first daily dose): 2 timepoints from the control (3/sex) and 6 timepoints from the test groups (3/sex/group) for a total of 456 samples. The TK report will include assessment of TK parameters such as C_{max}, t_{max}, AUC, dose proportionality for two analytes and single dose route.

Terminal procedures will include full gross necropsy and tissue collection on all animals and standard histopathology (up to 73 sections) on all animals. Statistical analyses will cover survival and tumour statistics (trend, pairwise, and graphs).

Study population:

Hemizygous CByB6F1-Tg(HRAS)2Jic mice aged approximately 7 weeks at receipt. Total population: 205/sex (hemizygous), 243/sex (wild type), including spares of 15/sex (hemizygous) and 15/sex (wild type). TK animals: 120/sex (wild type).

Milestones:

Study start: Q4 2023

Final report: Q1 2025

M2 Transgenic Mouse Carcinogenicity Study

Study short name and title:

M2 Transgenic Mouse Carcinogenicity Study

A 26-week Oral Gavage Carcinogenicity Study of M2 (Ganaxolone Metabolite) in Hemizygous CByB6F1-Tg(HRAS)2Jic Mice

Rationale and study objectives:

In addition to the 6-month toxicity study in rats, a 6-month carcinogenicity study in mice is planned to further evaluate mortality and morbidity, terminal histopathology, and tumour statistics in order to address the safety concern of long-term use. Study results will help support the long-term safety of M2 (GNX metabolite) in humans.

Study design:

Compliance: GLP

Pretreatment period: approximately 10 days

Dosing Regimen:

- M2 (twice daily [12 hours apart] for 182 days).
- Positive control (three times during Week 1)

Route of Administration: oral gavage (M2); positive control dosed via IP injection

Mortality/Morbidity: Twice daily

Detailed observations: Weekly and at termination on all main animals

Cage-side Observations: Daily on all animals

Body Weight: Day 4, weekly, and at termination on all animals

Clinical Pathology Parameters: A blood sample will be collected at termination from all animals and a blood smear will be prepared. Slide review will only by performed if necessary.

Toxicokinetic sample collection will be conducted on Days 1 and 180 (relative to the first daily dose): 2 timepoints from the control (3/sex) and 6 timepoints from the test groups (3/sex/group) for a total of 456 samples. The TK report will include assessment of TK parameters such as C_{max}, t_{max}, AUC, dose proportionality for two analytes and single dose route.

Terminal procedures will include full gross necropsy and tissue collection on all animals and standard histopathology (up to 73 sections) on all animals. Statistical analyses will cover survival and tumour statistics (trend, pairwise, and graphs).

Study population:

Hemizygous CByB6F1-Tg(HRAS)2Jic mice aged approximately 7 weeks at receipt. Total population: 205/sex (hemizygous), 243/sex (wild type), including spares of 15/sex (hemizygous) and 15/sex (wild type). TK animals: 120/sex (wild type).

Milestones:

Study start: Q4 2025

Final report: Q4 2026

M2 Chronic Toxicity Study

Study short name and title:

M2 Chronic Toxicity Study

A 26-Week Oral Gavage Toxicity Study of M2 (Ganaxolone metabolite) in the Albino Rat Followed by a 14-Day Recovery

Rationale and study objectives:

The M2 metabolite is not formed in any of the non-clinical species used for toxicity testing. In rats, M2 was found only at small levels relative to humans after repeated GNX administration. Following a recently completed 28-day toxicity study of the M2 metabolite in adult rats (Study 1020-7461), a 6-month repeat dose-toxicity study is planned to further evaluate treatment-related clinical signs, M2 exposure and accumulation, and gender differences in order to address the safety concern of long-term use. Study results will help support the long-term safety of GNX and its metabolites in humans.

Study design:

Compliance: GLP
Regimen: once daily for 26 weeks followed by a 2-week recovery period.
Route of administration: oral gavage
Spares: 10/sex
Pre-treatment period: 2 weeks
Mortality/Morbidity: twice daily
Detailed observations: weekly, excluding TK animals, starting 1 week prior to dosing
Body weight: weekly
Food consumption: weekly starting Day -1, excluding TK animals
Ophthalmology (excluding TK animals): pre-test, Week 26, and at the end of recovery if treatment-related findings are noted.
Clinical Pathology parameters:

- haematology, coagulation, clinical chemistry: at termination (standard parameters), excluding TK animals
- urinalysis: week 26 and at the end of recovery (standard parameters), excluding TK animals

Toxicokinetic sample collection will be conducted on Days 1 and 182: 2 time points from the control animals (3/sex) and 6 time points from the test groups (3 rats/sex/group) for a total of 240 samples. All TK animals will be discarded without further evaluation following euthanasia. The TK report will include assessment of TK parameters such as C_{max}, t_{max}, AUC, dose proportionality for 1 matrix, 1 analyte, 2 occasions and 1 dose route.

Terminal procedures will be conducted on Days 183 and 196 as follows:

- Macroscopic examination, organ weights and tissue retention
- Histology: control and high groups processed to slide, gross lesions (all groups); all other tissues retained
- Histopathology examination: control and high dose (standard tissues).

Study population:

Sprague Dawley rats aged 4-8 weeks at arrival will be studied; 110 each of male and female.

Milestones:

Study Start: March 2023

Final Report: Q4 2024

M2 Embryo-foetal Development Study

Study short name and title:

M2 Embryo-foetal Development Study

Rationale and study objectives:

The embryo-foetal development study is designed to detect potential adverse effects of the M2 metabolite of GNX on pregnant female rats and the development of embryos and foetuses after receiving M2 during organogenesis. The study results will be used to assess any potential risks for use of GNX in pregnant women or the developing human embryo and foetus.

Study design:

Compliance: GLP
Dosing Regimen: Daily administration on gestation days (GD) 6 to 17, inclusive
Pre-treatment Period: Pregnant rats will acclimate until appropriate gestation day for start of dose administration Route of Administration: Oral (gavage)
Toxicokinetics: Bioanalytical samples will be collected from 3 rats per test item group at each of 6 time points and at 1 time point from 3 control animals on the first and last days of dose administration. Animals will be euthanized and discarded following final blood collection, pregnancy status only. Total of 114 samples collected.
Mortality/Viability: Twice daily
Detailed Clinical Observations: Once prior to dosing and on GD 6, 9, 12, 15, 18 and 21
Cage-Side Observations: Predose on dosing days, once daily on non-dosing days
Post-dose/Cage-Side Observations: Once following each dose
Body Weight: Once prior to dosing and on GD 6, 9, 12, 15, 18 and 21 Food Consumption: GD 6, 9, 12, 15, 18 and 21 (TK animals excluded)
Gross Necropsy: Necropsy with macroscopic examination on GD 21
Uterine Examination: Determination of pregnancy status, examination of placentas, evaluation for number and distribution of corpora lutea, implantation sites, live and dead foetuses, and early and late resorptions. Gravid uterus weights recorded at scheduled euthanasia.
Foetal Observation: Foetal weight, foetal sex and examination for external (all foetuses), approximately 50% for visceral (fresh body and fixed head) and approximately 50% for skeletal changes, with representative photos of gross lesions/foetal abnormalities where applicable.
Study population: 109 sexually mature time-mated female Sprague Dawley rats

Milestones:

Study Start: Q1 2024

Final report: Q4 2024

Weight of Evidence Assessments

Weight of evidence assessments are planned to coincide with the final study report of the 6-month repeat-dose toxicity study with M2. These WoE assessments are post-authorisation measures to evaluate long term safety and the need for further characterisation.

Milestones:

WoE assessment for the need for a 2-year carcinogenicity study in rats with GNX – Q4 2024

WoE assessment for the need for a 2-year carcinogenicity study in rats with M2 – Q4 2024

WoE assessment for the need for a juvenile toxicity study with M2 – Q4 2024

M17 in vitro DDI Studies

Study short name and title:

M17 in vitro DDI Studies

An in vitro assessment of the drug interaction potential of the M17 metabolite as a perpetrator for major drug metabolising enzymes and transporters

Rationale and study objectives:

The in vitro studies are designed to determine if the M17 sulphated metabolite has the potential to cause DDIs.

Study design:

Plasma stability study in human and rat plasma. M17 stability will be measured at a single concentration (2 μM) in K2EDTA plasma matrix. Stability will be measured at multiple time points from 0-4 hrs at 37ºC and the percent remaining relative to Time 0 will be reported.

Time dependent CYP450 inhibition. CYP450 isozymes from human liver microsomes will be used. IC_{50} determinations will be derived from 10 M17 concentrations (0.003 – 100 μM). M17 will be preincubated for 30 min prior to addition of substrates. The CYP450 substrates to be used are as follows:

- 1A2 (phenacetin)
- 2B6 (buproprion)
- 2C8 (amodiaquine)
- 2C9 (diclofenac)
- 2C19 (mephenytoin)
- 2D6 (dextromethorphan)
- 3A4 (midazolam and testosterone)

There will be a single control inhibitor for each isozyme. Percent inhibition will be calculated relative to full activity and no activity control conditions, using peak area ratios.

Protein Binding, (Equilibrium Dialysis) will be conducted from plasma protein derived from rat and human. Protein binding will be assessed in plasma and in brain homogenate. M17 protein binding to be conducted at a single concentration (5 μM), at 6 hrs and at 37ºC. Warfarin will be used as positive control. Percent binding calculated based on analytic area ratios.

CYP450 Induction

M17 will first be evaluated for cytotoxicity in human hepatocytes. M17 will be tested in concentration response format (0.01 – 100 μM) and IC_{50} determined. CYP Induction will be conducted in human hepatocytes at 3 concentrations of M17 (TBD). Three CYP isozymes will be tested: 1A2 (omeprazole control inducer), 2B6 (phenobarbital control inducer), 3A4 (rifampicin

control inducer). Induction will be measured after 48 hrs of incubation and the per cent induction calculated relative to vehicle control.

CYP450 Reaction Phenotyping for M17 will be conducted in human liver microsomes with inhibitors. The metabolic stability of M17 in presence and absence of known inhibitors. Multiple time points for half-life calculation will be tested (0-120 min; 37º C).

The following CYP450 isozymes will be tested:

- Furafylline (1A2)
- 2-phenyl-2-(1-piperidinyl)propane (2B6)
- Quercetin (2C8)
- Sulfaphenazole (2C9)
- Omeprazole (2C19)
- Quinidine (2D6)
- Ketoconazole (3A4)

Caco-2 Permeability (bi-directional) with Preliminary Transporter Assessment [Pgp (MDR1) and BCRP] (SDL-2). These permeability studies will be conducted using human Caco-2 cells and measuring bi-directional flux (A-B and B-A). A single M17 concentration will be tested (10 μM) at a single time point (2 hrs). Transporter inhibitors for Pgp (MDR1 and BCRP) will also be incorporated into the assay.

Milestones:

Final report Q4 2023

M17 in vivo PK Study with Brain Penetrance

Study short name and title:

M17 in vivo PK Study with Brain Penetrance

A central nervous system (CNS) distribution study of the major human plasma metabolite, M17 (sulphate-conjugated metabolite), in rat

Rationale and study objectives:

The in vivo studies are designed to determine if M17 is capable of penetrating into the brain and, if so, the levels of M17 in the brain.

Study design:

M17 will be evaluated for pharmacokinetic characteristics and brain penetrance properties. The in vivo PK study will be conducted in adult male, Sprague-Dawley rats. Eighteen rats will be included in the study. There will be 3 rats per time point. Rats will be bled and brains collected once at the timepoint described in the table below. Rats will be administered a single dose GNX level of M17 (10 mg/kg). The route of administration will be intraperitoneal (IP) to avoid intestinal absorption.

Group	Time of Blood and Brain Collection (hrs)	N
1	0.5	3

2	1	3
3	2	3
4	4	3
5	8	3
6	24	3

Plasma will be prepared for collected blood. Prior to brain dissection, animals will be perfused with saline to remove excess blood from collected brain. Brains will be homogenised in appropriate homogenisation buffer and M17 extracted. Plasma and brain levels of M17 will be measured by standard bioanalytical measures (e.g., LC/MS/MS). PK parameters will be analysed using WinNonlin PK non-compartmental analysis.

Milestones:

Final report Q4 2023

III.3 Summary Table of additional Pharmacovigilance activities

Table 14: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Participation in EURAP (European Registry of Antiepileptic Drugs and Pregnancy) Observational Study Planned	To evaluate the risk of GNX during pregnancy	Missing information on use in pregnancy and during breast-feeding	Regular updates	Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs, when available.

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Study LLF001 (CANDID observational study) Endpoint Enabling Study in Cyclin-dependent kinase-like 5 Deficiency Disorder Planned	To assess the clinical characteristics of CDD across multiple domains and to understand the longitudinal trajectories of CDD patients across the various clinical outcomes (eg, related to seizures, sleep, behaviour, cognition, global development, and quality of life) To conduct regular safety assessments, including adverse events.	Long term safety	Milestone reports after 50 participants have completed the first-year visit, and once approximately 100 participants have completed the first year Annual updates (DLP in line with that of the ganaxolone PSUR [17 March])	First annual update May 2024, and then annually in line with the ganaxolone PSUR reporting dates*
CDD-IPR-CDD-01 CDKL5 Deficiency Disorder International Patient Registry Planned	The primary objective of the registry is to collect and enable sharing of real-world demographic, clinical, PRO, and treatment data collected from patients with CDD or their legal guardians and ultimately, their clinicians. Secondarily, the CDKL5 Registry aims to aid in establishing best practices in standard of care for CDD, to inform clinical study design by collecting real-world data and providing access to the scientific and research community, to enable research through data sharing, to understand patient needs and quality of life factors, and to enable rapid recruitment by connecting patients to clinical trials.	Long term safety (including delayed sexual maturation and growth)	Six monthly updates (DLPs in line with those of the ganaxolone PSUR (17 March and 17 September)	First 6 monthly update May 2024, and then every six months in line with the ganaxolone PSUR reporting dates*
GNX Steady-State Metabolite Study Planned	To characterise the GNX metabolite pattern at steady state	Long term safety	Re-analysis of 1042-TQT-1001 study (if feasible) PK study (if relevant)	Q4 2023 Q1 2025

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
GNX Transgenic Mouse Carcinogenicity Study A 26-week Oral Gavage Carcinogenicity Study of Ganaxolone (GNX) in Hemizygous CByB6F1-Tg(HRAS)2Jic Mice Ongoing	To further evaluate mortality and morbidity, terminal histopathology, and tumour statistics for GNX	Long term safety (including delayed sexual maturation and growth)	Study start Final report	Q4 2023 Q1 2025
M2 Transgenic Mouse Carcinogenicity Study A 26-week Oral Gavage Carcinogenicity Study of M2 (Ganaxolone Metabolite) in Hemizygous CByB6F1-Tg(HRAS)2Jic Mice Planned	To further evaluate mortality and morbidity, terminal histopathology, and tumour statistics for M2 (GNX metabolite)	Long term safety (including delayed sexual maturation and growth)	Study start Final report	Q4 2025 Q4 2026
M2 Chronic Toxicity Study A 26-Week Oral Gavage Toxicity Study of M2 (Ganaxolone metabolite) in the Albino Rat Followed by a 14-Day Recovery Ongoing	To further evaluate treatment-related clinical signs, M2 exposure and accumulation, and gender differences	Long term safety (including delayed sexual maturation and growth)	Study start Final report	March 2023 Q4 2024

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
M2 Embryo-foetal Development Study Planned	To detect potential adverse effects of the M2 metabolite of GNX on pregnant female rats and the development of embryos and foetuses after receiving M2 during organogenesis.	Use in pregnancy	Study start Final report	Q1 2024 Q4 2024
WoE assessment	To evaluate the need for a 2-year carcinogenicity study in rats with GNX	Long term safety	Final report	Q4 2024
WoE assessment	To evaluate the need for a 2 year carcinogenicity study in rats with M2	Long term safety	Final report	Q4 2024
WoE assessment	To evaluate the need for a juvenile toxicity study with M2	Long term safety	Final report	Q4 2024
M17 in vitro DDI Studies	To determine if the M17 sulphated metabolite has the potential to cause DDIs.	Long term safety	Final report	Q4 2023
M17 in vivo PK Study with Brain Penetrance	To determine if M17 is capable of penetrating into the brain and, if so, the levels of M17 in the brain.	Long term safety	Final report	Q4 2023

* list-european-union-reference-dates-frequency-submission-periodic-safety-update-reports-psurs_.xlsx (live.com))

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 15: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Long term safety (including sexual maturation and growth) (Important potential risk)	Routine risk communication: • SmPC section 5.3 informed of decreased bodyweight gain and a delay in sexual maturation in juvenile animal studies Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine • ZTALMY treatment initiated and supervised by physicians experienced in the treatment of epilepsy
Suicidal behaviour and ideation (Important potential risk)	Routine risk communication: • Warning in SmPC section 4.4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning that suicidal behaviour and ideation have been reported in patients treated with AEDs in several indications and the available data do not exclude the possibility of an increased risk with GNX in SmPC section 4.4 • Recommendation to advise caregivers to monitor patients for signs of suicidal behaviour and ideation, or self-harm behaviour and to seek medical advice should any signs of suicidal behaviour and ideation, or self-harm emerge in SmPC section 4.4 • Warning for the patient (or caregiver) to contact their doctor straightaway if the patient has noticed unusual changes in their mood or behaviour, or had thoughts of harming or killing themselves, in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine • ZTALMY treatment initiated and supervised by physicians experienced in the treatment of epilepsy
Use in pregnancy and during breastfeeding (Missing information)	Routine risk communication: • Information that there are limited data on the use of GNX in pregnant women in SmPC section 4.6 • Information that GNX and its metabolites are excreted in human milk but the effect of GNX on breastfed newborns/infants is unknown in SmPC section 4.6 Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	• Recommendation not to use GNX during pregnancy and in woman of childbearing potential not using contraception in SmPC section 4.6 • Recommendation to decide whether to discontinue breastfeeding or to discontinue ZTALMY therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman, in SmPC section 4.6 • Warning for the patient not to take ZTALMY if pregnant or a women of child-bearing potential not using contraception, in PL section 2 • Warning for the patient not to use ZTALMY whilst breast-feeding unless the patient's doctor decides the benefits of taking ZTALMY outweighs any potential risks, in PL section 2. • Recommendation for the patient to ask their doctor or pharmacist for advice before taking this medicine if the patient is pregnant or breastfeeding, or thinks they may be pregnant, in PL section 2 Other routine risk minimisation measures beyond the Product Information: • Prescription only medicine • ZTALMY treatment initiated and supervised by physicians experienced in the treatment of epilepsy

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 16: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long term safety (including delay in sexual maturation and growth)	Routine risk minimisation measures: • *Information in SmPC section 5.3* • *Prescription only medicine* • *Prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *Study LLF001 (CANDID)* • *CDKL5 Deficiency Disorder International Patient Registry* • *GNX steady-state metabolite study* • *M2 chronic toxicity study* • *GNX Transgenic Mouse Carcinogenicity Study* • *M2 Transgenic Mouse Carcinogenicity Study* • *WoE assessments* • *M17 in vitro DDI Studies* • *M17 in vivo PK Study with Brain Penetrance*
Suicidal behaviour and ideation	Routine risk minimisation measures: • *Warning in SmPC section 4.4* • *Warning in PL section 2 in lay language* • *Prescription only medicine* • *Prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None*

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Use in pregnancy and during breastfeeding	Routine risk minimisation measures: • *Warning/information in SmPC section 4.6* • *Warning in PL section 2 in lay language* • *Prescription only medicine* • *Prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Pregnancy Notification and Outcome follow-up forms* Additional pharmacovigilance activities: • *EURAP Observational Study* • *M2 Embryo-foetal development study*

Part VI: Summary of the risk management plan

Summary of risk management plan for ZTALMY (Ganaxolone)

This is a summary of the risk management plan (RMP) for ZTALMY. The RMP details important risks of ZTALMY, how these risks can be minimised, and how more information will be obtained about ZTALMY's risks and uncertainties (missing information).

ZTALMY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ZTALMY should be used.

This summary of the RMP for ZTALMY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ZTALMY's RMP.

I. The medicine and what it is used for

ZTALMY is authorised for the adjunctive treatment of epileptic seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD) in patients 2 to 17 years of age. ZTALMY may be continued in patients 18 years of age and older (see SmPC for the full indication).
It contains ganaxolone as the active substance and it is given as an oral suspension.

Further information about the evaluation of ZTALMY's benefits can be found in ZTALMY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ztalmy.

II. Risks associated with the medicine and activities to minimise or further characterise these risks

Important risks of ZTALMY, together with measures to minimise such risks and the proposed studies for learning more about ZTALMY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of ZTALMY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ZTALMY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ZTALMY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Long term safety (including delayed sexual maturation and growth) • Suicidal behaviour and ideation
Missing information	• Use in pregnancy and during breastfeeding

II.B Summary of important risks

Important potential risk 1:	**Long term safety (including delayed sexual maturation and growth)**
Evidence for linking the risk to the medicine	Decreased body weight gain and a significant delay in sexual maturation was observed in non-clinical studies. However, the observed delay in sexual maturation did not result in any effects on reproductive capability as adults. The human relevance of this finding is unknown as there is insufficient clinical safety data to assess long term use effects currently.
Risk factors and risk groups	Unknown
Risk minimisation measures	• *Information in SmPC section 5.3* • *Prescription only medicine* • *Prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study LLF001 (CANDID); CDKL5 Deficiency Disorder International Patient Registry; GNX Steady-State Metabolite study, GNX Transgenic Mouse Carcinogenicity Study, M2 Transgenic Mouse Carcinogenicity Study, M2 chronic toxicity study, WoE assessments, M17 in vitro DDI Studies, M17 in vivo PK Study with Brain Penetrance See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 1: Suicidal behaviour and ideation	
Evidence for linking the risk to the medicine	In a comprehensive search of the entire GNX clinical development programme including completed and ongoing studies, a total of 9 reports of suicidality were identified in >1600 subjects exposed to GNX. In completed placebo-controlled studies, 1 (0.1%) event of suicidality occurred in the GNX group while 3 events (0.3%) occurred in the placebo group.
Risk factors and risk groups	According to the World Health Organisation (WHO 2021), more than 700,000 people die due to suicide every year in the general population, with suicide being the fourth leading cause of death in 15 to 19-year-olds. While suicide is relatively rare in children, in Europe, where youth suicide rates are tending to decrease, suicide is ranked as the second most frequent cause of death in those aged 10-19 years. In general, the presence of a mental disorder substantially increases suicide risk but moments of crisis with a breakdown in the ability to deal with life stresses (such as education, living situation, or peer pressure) can have a contributory role (Bilson 2018). It is unknown if there is a background tendency towards suicidal behaviour and ideation in the specific CDD population.
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4* • *Warning in PL section 2 in lay language* • *Prescription only medicine; prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in pregnancy and during breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: • *Warning/information in SmPC section 4.6* • *Warning in PL section 2 in lay language* • *Prescription only medicine; prescribed by physicians experienced in the treatment of epilepsy* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EURAP (European Registry of Antiepileptic Drugs and Pregnancy) Observational Study, M2 Embryo-foetal development study See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of ZTALMY.

II.C.2 Other studies in post-authorisation development plan

EURAP Observational Study

Purpose of the study:

The primary objective of participation in the EURAP observational study is to evaluate and determine the comparative degree of safety of GNX in pregnant women, with reference to and in combination with other antiepileptic drugs, including the evaluation of any specific pattern of major malformations, dose-effect relationships and other risk factors. Participation in the EURAP observational study will help to provide meaningful conclusions with respect to the safety of GNX in pregnancy through an international collaboration generating large numbers of female patients of childbearing age.

Study LLF001 (CANDID)

Purpose of the study:

The objectives of this global study are to assess the clinical characteristics of CDD across multiple domains and to understand the longitudinal trajectories of CDD patients across the various clinical outcomes. The study will assess clinical outcomes related to seizures, sleep, behaviour, cognition, global development, and quality of life as well as regular safety assessments, including adverse events. Adverse events of particular interest are infection-related adverse events, aspiration pneumonia, gastrointestinal-related adverse events, and somnolence. As this is an exploratory observational study, no formal statistical hypothesis testing is planned, and data will be presented using descriptive statistics.

CDKL5 Deficiency Disorder International Patient Registry

Purpose of the study:

The primary objective of the patient registry is to collect and enable sharing of real-world demographic, clinical, patient reported outcome (PRO), and treatment data collected from patients with CDD or their legal guardians, and ultimately, their clinicians. Secondarily, the CDKL5 Registry aims to aid in establishing best practices in standard of care for CDD, to inform clinical study design by collecting real-world data and providing access to the scientific and research community, to enable research through data sharing, to understand patient needs and quality of life factors, and to enable rapid recruitment by connecting patients to clinical trials.

GNX Steady-State Metabolite Study

Purpose of the study:

To determine the amount of various GNX metabolites in the blood following administration of repeated doses of GNX to humans. The study results will be used to assess the long term safety of GNX.

GNX Transgenic Mouse Carcinogenicity Study

Purpose of the study:

This 6-month carcinogenicity study in mice is planned to further evaluate mortality and morbidity, terminal histopathology, and tumour statistics to address the safety concern of long-term use. Study results will help support the long-term safety of GNX in humans.

M2 Transgenic Mouse Carcinogenicity Study

Purpose of the study:

This 6-month carcinogenicity study in mice is planned to further evaluate mortality and morbidity, terminal histopathology, and tumour statistics to address the safety concern of long-term use. Study results will help support the long-term safety of M2 (GNX metabolite) in humans.

M2 Chronic Toxicity Study

Purpose of the study:

This 6-month repeat dose-toxicity study is planned to further evaluate treatment-related clinical signs, M2 exposure and accumulation, and gender differences in order to address the safety concern of long-term use. Study results will help support the long-term safety of GNX and its metabolites in humans.

M2 Embryo-foetal Development Study

Purpose of the study:

The embryo-foetal development study is designed to detect potential adverse effects of the M2 metabolite of GNX on pregnant female rats and the development of embryos and foetuses after receiving M2 during the period when organs are formed. The study results will be used to assess any potential risks for use of GNX in pregnant women or the developing human embryo and foetus.

Weight of Evidence (WoE) Assessments

Following completion of the M2 chronic toxicity study, WoE assessments will be made to determine whether any further carcinogenicity or juvenile studies are necessary to evaluate long-term safety.M17 in vitro DDI Studies

To determine if the M17 sulphated metabolite of GNX has the potential to cause drug-drug interactions that may impact the long- term safety.

M17 in vivo PK Study with Brain Penetrance

To determine if M17 sulphated metabolite of GNX is capable of penetrating into the brain and, if so, the levels of M17 in the brain.

List of references for the RMP Public Summary

Bilson J. Suicide and youth: risk factors. Front Psychiatry. 2018;9:540.

World Health Organisation. Fact-sheet: Suicide. 2021. Available at https://www.who.int/news-room/fact-sheets/detail/suicide

Part VII: Annexes

Table of contents

Annex 1: Specific adverse drug reaction follow-up forms

A pregnancy follow-up questionnaire as a routine pharmacovigilance activity is being developed to collect and evaluate specific data related to the following safety concern (missing information) in the post-marketing period:

- Use in pregnancy and during breastfeeding
    - Post-Marketing Pregnancy Notification Form
    - Post-Marketing Pregnancy Outcome Form

Post-Marketing Pregnancy Notification Form

DRUG SAFETY NAVIGATOR

PREGNANCY NOTIFICATION FORM MARINUS PHARMACEUTICALS

Patient initials	Patient Date of birth	Patient age
☐☐☐	☐☐ / ☐☐ / ☐☐☐☐ (MM / DD / YYYY)	☐☐ years

Case ID: YYCC_MAR_XXX

This form should be completed within 24 hours of awareness of a pregnancy that occurs after a patient received a Marinus product. Please complete and send this form to:

Marinus Safety email: PVG@drugsafetynavigator.com

Pregnancy itself is not an adverse event. However, all reports of pregnancy must be reported via the Pregnancy Notification Form to Marinus for safety evaluation.

A spontaneous abortion is always considered to be a serious adverse event and should be reported to DSN within 24 hours of awareness. All reported pregnancy cases will be followed up until outcome.

PREGNANCY-RELATED ADVERSE EVENT/PRODUCT COMPLAINT (AE/PC)
Was an AE/PC associated with this pregnancy? ☐yes ☐no If yes, please submit an AE/SAE form to pvg@drugsafetynavigator.com and link both forms (this pregnancy notification form with case ID YYCC_MAR_XXX is linked with AE/SAE form with case ID xxx).

PATIENT'S RELEVANT MEDICAL/FAMILY HISTORY	
Patient's Date of last dose of Ganaxolone prior to pregnancy:	Date of Last Menstrual Period:
Estimated Date of Delivery:	
Was the Patient using a method of contraception? ☐yes ☐no If yes, please specify:	
Type of Conception; Check one: ☐ Normal (includes use of fertility drugs) ☐ IVF (in-vitro fertilization)	

Relevant Laboratory Tests and Procedures (e.g., ultrasound, amniocentesis and chorionic villi sampling) including dates of tests and results if available:

DRUG SAFETY NAVIGATOR

PREGNANCY NOTIFICATION FORM

MARINUS PHARMACEUTICALS

Patient initials	Patient Date of birth	Patient age
☐☐☐	☐☐ / ☐☐ / ☐☐☐☐ (MM / DD / YYYY)	☐☐ years

Number of Previous Pregnancies:
☐☐ Preterm ☐☐ Full Term

If applicable, record the number in the appropriate categories below:
☐☐ Normal Births ☐☐ Spontaneous Abortion ☐☐ Still Birth

☐☐ Elective Abortion ☐☐ Children with birth abnormalities ☐☐ Other (describe)

Please provide details of any birth abnormalities or other relevant information:

Are there any additional factors that may have an impact on the outcome of this pregnancy?
☐ yes
☐ No
If yes, please specify:

FATHER'S RELEVANT MEDICAL/FAMILY HISTORY

Include habitual exposures such as alcohol/substance abuse, chronic illnesses, familial birth defects/genetic/chromosomal disorders and medication use:

DSN-SAF-TP017:01 Post-Marketing Pregnancy Notification Form Effective 15-Apr-2021
2021 Drug Safety Navigator: Proprietary and Confidential Page 2 of 3

DRUG SAFETY NAVIGATOR

PREGNANCY NOTIFICATION FORM

MARINUS PHARMACEUTICALS

Patient initials	Patient Date of birth	Patient age
☐☐☐	☐☐ / ☐☐ / ☐☐☐☐ (MM / DD / YYYY)	☐☐ years

PATIENT'S DRUG EXPOSURE

In the following table, list all medications the patient (**Mother**) received 30 days prior to conception and up to present (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.).
Enter the Marinus product details on the first line.

Drug Name (Trade Name Preferred)	Route of Admin. or Formulation	Total Daily Dose	Units	Started Pre-Study	Start Date	Stop Date	Ongoing Y=yes N=no	Indication
Ganaxolone								

REPORTER INFORMATION

Name:	Title:	Specialty:
Address:		
City:	State/Province:	Country:
Telephone:	Postal Code:	Name of Clinic/ Facility:

Reporter's Signature *(confirming that the data on these pages are accurate and complete):*	**Date:**
Reporter's Name *(print):*	

Post-Marketing Pregnancy Outcome Form

DRUG SAFETY NAVIGATOR

MARINUS PHARMACEUTICALS

Pregnancy Outcome Form

MOTHER DETAILS:

Patient initials	Patient Date of birth	Patient age
☐☐☐	☐☐/☐☐/☐☐☐☐ (MM / DD / YYYY)	☐☐ years

Case ID: YYCC_MAR_XXX

This form should be completed within 24 hours of awareness of the OUTCOME of a pregnancy that occurred after a patient received a Marinus product. Please complete and send this form to:

Marinus Safety email: PVG@drugsafetynavigator.com

The outcome of a pregnancy itself is not an adverse event. However, all reports of pregnancy outcomes must be reported via the Pregnancy Follow-Up Form to Marinus for safety evaluation.

A spontaneous abortion is always considered to be a serious adverse event and should be reported to DSN within 24 hours of awareness. All reported pregnancy cases will be followed up four weeks after projected due date and four weeks thereafter and reported via this Pregnancy Follow-Up form.

One form should be completed per fetus (e.g. If a subject is carrying twins, a form should be completed for each twin)

Early Termination: *Check if applicable*

- ☐ Stillbirth
- ☐ Fetal Death
- ☐ Method Used for Delivery: *Specify*

☐ Spontaneous Abortion
☐ Elective Abortion
☐ Other: *Specify*

Fetal Neonatal Status

- ☐ Normal
- ☐ Birth Defect (i.e. Structural Chromosomal Disorder)
- ☐ Other Disorder (i.e. Non-structural, premature birth, intrauterine death, stillbirth)

If birth defects are diagnosed, is the origin of the defect known? ☐ Yes ☐ No If yes, *specify:*

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DRUG SAFETY NAVIGATOR

MARINUS PHARMACEUTICALS

Pregnancy Outcome Form

MOTHER DETAILS:

Patient initials ☐☐☐

Patient Date of birth ☐☐/☐☐/☐☐☐☐ (MM / DD / YYYY)

Patient age ☐☐ years

PREGNANCY-RELATED ADVERSE EVENT/PRODUCT COMPLAINT (AE/PC)

Was an AE/PC associated with this pregnancy? ☐yes ☐no

If yes, please submit an AE/SAE form to pvg@drugsafetynavigator.com and link both forms (this pregnancy notification form with case ID YYCC_MAR_XXX_is linked with AE/SAE form with case ID xxx).

Date of Birth/miscarriage/termination (DD MMM YYYY): ☐☐/☐☐☐/☐☐☐☐

Gestational weeks at Birth/Miscarriage/termination: ☐☐

Infants Gender: ☐Female ☐Male ☐Unknown

Length ☐☐.☐cm | Weight ☐☐☐☐.☐☐g

Apgar Score (0-10) ☐☐ First Assessment ☐☐ Second Assessment

Additional Details (Current labor/delivery/discharge notes, etc.)

DRUG EXPOSURE DURING PREGNANCY

Date of last dose of Ganaxolone (DD MMM YYYY): ☐☐/☐☐☐/☐☐☐☐

In the following table, list all medications the patient (**Mother**) received 30 days prior to conception and up to OUTCOME of the Pregnancy (e.g. prescription, OTC, vaccines, recreational, alcohol, etc.).

DRUG SAFETY NAVIGATOR

MARINUS PHARMACEUTICALS

Pregnancy Outcome Form

Drug Name	Route of Administration/ Formulation	Total Daily Dose	Started Pre-Study: Y=yes N=no	Start Date DD-MMM-YYYY	End Date DD-MMM-YYYY	Ongoing? Y=yes N=no	Indication

MOTHER DETAILS:

Patient initials | **Patient Date of birth** (MM / DD / YYYY) | **Patient age** ____ years

REPORTER INFORMATION		
Name:	Title:	Specialty:
Address:		
City:	State/Province:	Country:
Telephone:	Postal Code:	Name of Clinic/ Facility:

Reporter's Signature *(confirming that the data on these pages are accurate and complete):*	**Date:**
Reporter's Name *(print):*	

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Annex 2: Details of proposed additional risk minimisation activities

Not applicable