RISK MANAGEMENT PLAN

ONTOZRY (cenobamate)

RMP Version number	4.1
Date lock point for this RMP	30NOV2023
Date of final sign off	08Apr2024
Rationale for submitting an updated RMP	Reclassification of the Important potential risk “Suicidality (class effect)”, as requested in the PRAC recommendation of procedure EMEA/H/C/PSUSA/00010921/202303.
Summary of significant changes in this RMP	Reclassification of the Important potential risk “Suicidality (class effect)” as an Important identified risk re-named as “Suicidality”.
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Version 1.0 approved on 26MAR2021 (EC decision) Version 2.0 (GB-specific) approved on 04JUN2021 (MHRA) Version 3.0 approved on 07JUL2022 (CHMP Opinion) and 25JAN2023 (MHRA).

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PART I: PRODUCT OVERVIEW

Table Part I.1.- Product Overview

Active substance (INN or common name)	Cenobamate
Pharmacotherapeutic group (ATC Code)	Antiepileptics, Other antiepileptics, ATC Code: N03AX25
Marketing Authorisation Holder	Angelini Pharma SpA (formerly Arvelle Therapeutics Netherlands B.V.)
Medicinal products to which this RMP refers	6
Invented name in the European Economic Area (EEA)/GB	Ontozry
Marketing authorisation procedure	Centralised in EU / National in GB and CH
Brief description of the product	Chemical class: Tetrazole alkyl carbamate derivative
	Cenobamate is a small molecule with a dual mechanism of action. It is a positive allosteric modulator of subtypes of the γ-aminobutyric acid (GABAA) ion channel, that does not bind to the benzodiazepine binding site. Cenobamate has also been shown to reduce repetitive neuronal firing by enhancing the inactivation of sodium channels and by inhibiting the persistent component of the sodium current. The precise mechanism of action by which cenobamate exercises its therapeutic effects in patients with focal-onset seizures is unknown.
	Important information about its composition: Each 12.5 mg tablet contains 39.7 mg lactose monohydrate. Each 25 mg film-coated tablet contains 79.3 mg lactose monohydrate. Each 50 mg film-coated tablet contains 158.7 mg lactose monohydrate. Each 100 mg film-coated tablet contains 108.7 mg lactose monohydrate. Each 150 mg film-coated tablet contains 163 mg lactose monohydrate. Each 200 mg film-coated tablet contains 217.4 mg lactose monohydrate.
Hyperlink to the Product Information	Section 1.3.5 of the eCTD
Indication in the EEA/GB/CH	Current in EEA: Cenobamate is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products.
	Current in GB: Cenobamate is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic products.
	Current in CH: Ontozry is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who are not adequately controlled despite prior treatment with at least 2 anti-epileptic medicinal products.
	Proposed: not applicable
Dosage in the EEA/GB/CH	Current: The recommended starting dose of cenobamate is 12.5 mg per day, titrated gradually to the recommended target dose of 200 mg per day. Based on clinical response, dose may be increased to a maximum of 400 mg per day. Some patients, who do not reach optimal seizure control, may benefit from doses above 200 mg (increased by increments of 50 mg/day every two weeks) up to a maximum of 400 mg daily.

	Proposed: not applicable
Pharmaceutical forms and strengths	Current: Tablets Film-coated tablets 12.5 mg tablets: Uncoated round white to off-white tablets with AV on one side and ‘12’ on the other side 25 mg film-coated tablets: Film-coated round brown tablets with AV on one side and ‘25’ on the other side 50 mg film-coated tablets: Film-coated round yellow tablets with AV on one side and ‘50’ on the other side 100 mg film-coated tablets: Film-coated round brown tablets with AV on one side and ‘100’ on the other side 150 mg film-coated tablets: Film-coated oval light orange tablets with AV on one side and ‘150’ on the other side 200 mg film-coated tablets: Film-coated oval light orange tablets with AV on one side and ‘200’ on the other side
	Proposed: not applicable
Will the product be subject to additional monitoring in the EU/GB/CH?	Yes

PART II: SAFETY SPECIFICATION

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

Indication:

EEA: Adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products.

GB: Adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite treatment with at least 2 anti-epileptic products.

CH: Adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who are not adequately controlled despite prior treatment with at least 2 anti-epileptic medicinal products.

Incidence and prevalence:

Epilepsy is one of the most prevalent serious neurological conditions. It affects about 70 million people worldwide. Each year, 16 to 134 new-onset epilepsy cases per 100,000 people are diagnosed (Laxer 2014). Estimates for drug resistant epilepsy range from 22.5% to 40%. In a population-based study conducted in Western Europe, the epilepsy in 22.5% of all patients was found to be drug-resistant (Picot 2008). A longitudinal study estimated 30-40% of patients with epilepsy become drug resistant (Kwan 2000). In recent meta-analysis, the pooled prevalence of drug resistant epilepsy in newly diagnosed epilepsy patients was found to be 25% (95% confidence interval [CI] 17–32%) (Xue-Ping 2019).

Importantly, an evaluation in drug-resistant epilepsy over time found that there has been very little change from 1993 (53/142, 37%) to 2003 (247/684, 36%) to 2014 (378/969, 39%), despite the emergence of new therapies (Chen 2018).

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

Epilepsy affects persons of all ages, races, and ethnicities, especially those with the lowest incomes (Epilepsy Research UK 2020; Newton 2012). Approximately 75% of epilepsy cases begin during childhood (Stafstrom 2015). The most common type of epilepsy in both adults and children is focal-onset seizures.

Risk factors for drug resistant epilepsy may include younger onset age, abnormal electroencephalogram (EEG) findings and neurological deficits or mental retardation at the time of diagnosis, symptomatic aetiology, high-frequency seizures, non-response to the first AED and certain epilepsy syndromes, such as West syndrome and Lennox-Gastaut syndrome (Xue-Ping 2019; Kalilani 2018).

Some patients with refractory epilepsy can be identified early in the course of disease rather than evolve over time and are more likely to have underlying structural cerebral abnormalities, to have had more than 20 seizures before treatment is initiated, and to have an inadequate response to the first antiepileptic drug (AED) prescribed (Kwan 2000). One study found that if the first 2 AEDs failed to control all seizures, the third AED regimen offered only a 4.1% additional probability of seizure freedom and from the fourth AED regimen onwards, each additional AED only added an approximate 1% or less probability of seizure freedom irrespective of the specific medications chosen (Chen 2018). The seizure free rate was higher in patients with generalized epilepsy (251/386, 65.0%) compared with focal epilepsy (856/1,409, 60.8%) after adjustment for age at onset and gender (p=0.036).

The main existing treatment options:

Control of epilepsy primarily focuses on suppressing seizure activity because the underlying condition is not curatively treatable.

The mechanism of action of AEDs is to decrease the electrical activity of the brain via preventing neurone depolarisation by blocking sodium or calcium channels, inhibiting excitation mediated by the neurotransmitter glutamate, or promoting inhibition via gamma-aminobutyric acid (GABA) (Stafstrom 2015).

Current treatments to achieve seizure freedom for drug resistant epilepsy are elusive despite the availability of more than 20 approved anti-seizure medications (ASMs) (Kwok 2017). These medications show a very modest success in achieving seizure freedom, in the range of 4% to 5% (Costa 2011, French 2012, French 2013; Steinhoff 2013; Ryvlin 2014; Biton 2014; Klein 2015; Ben-Menachem 2016; Biton 2017). A few other studies documented seizure-freedom rates of up to 12.4% (Peeters 2003; Gil-Nagel 2009; French 2013; French 2014; Chung 2014; Klein 2015).

Consistent with this report, substantial reductions in seizure frequency in patients using ≥2 AEDs are not common (French 2020) and the ability to achieve seizure freedom has been found to be disappointingly small (Beyenburg 2010).

Overall, second-generation antiseizure medications have failed to provide a superior efficacy to first-generation medication and to meaningfully reduce the proportion of individuals with pharmacoresistant epilepsy (Perucca 2020).

Because there is increasing evidence that seizure freedom will substantially improve prognosis (Beghi 2015), reduce the burden of disease, and even mortality, patients with drug refractory epilepsy should receive optimal treatment to give them the best chance of seizure freedom (Sander 2004).Therefore, a new AED with a favourable tolerability profile and high efficacy in achieving seizure freedom represents the ultimate unmet medical need in addressing the burden and suffering of people with drug refractory epilepsy.The choice of AED should be tailored to each patient, taking into account many factors including, but not limited to, age, gender, co-existent medical conditions, and the use of concomitant medications (Burakgazi 2016). The goal of treatment is to provide optimal seizure control while using the least possible number of medications (Burakgazi 2016). Typically, treatment with AEDs requires adjustment over time depending on the degree of seizure control and the patient's ability to tolerate the AED.

AEDs used in clinical practice against focal seizures (with or without secondary generalization) include carbamazepine, phenytoin, gabapentin, lacosamide, oxcarbazepine, pregabalin, tiagabine, vigabatrin, retigabine, and eslicarbazepine (Burakgazi 2016). AED of choice when the epilepsy syndrome has not yet been determined include valproate, benzodiazepines, perampanel, phenobarbital, primidone, lamotrigine, levetiracetam, topiramate, zonisamide, rufinamide, and felbamate (Burakgazi 2016).

Most often, treatment is initiated at a low dose and subsequently increased as needed in order to control seizures with the lowest possible therapeutic dose. Despite causing serious adverse reactions, first generation AEDs are still used as treatment for focal-onset seizures. Subsequent generations of AEDs have

been approved with different mechanisms of action and improved tolerability profiles but despite the availability of these new AEDs, overall outcomes in epilepsy have not improved over the last decades (Kwok 2017; Brodie 2018).

Management of patients with drug-resistant epilepsy is particularly challenging because it is not fully understood how or why pharmacoresistance develops in a particular patient (French 2007). When a first drug fails, further AEDs will be initiated (Stafstrom 2015). Polytherapy is usually offered after failure of 2 or 3 sequential monotherapies but may be considered earlier when prognostic factors indicate a difficult-to-treat form of epilepsy unlikely to respond fully to monotherapy.

Other treatment options such as surgery, devices, and a ketogenic diet are also considered for treatment-resistant epilepsy (Burakgazi 2016). In a randomised controlled trial, anterior temporal lobectomy was shown to be more effective than medical therapy, achieving seizure freedom in up to 70% of adults with refractory temporal lobe epilepsy (Wiebe 2001; Téllez-Zenteno 2005). In another study 28% of postsurgical patients not using AEDs were found to be seizure-free following anterior temporal lobectomy (de Tisi 2011). Other surgical procedures for epilepsy include resection of structural lesions (lesionectomy), corpus callosotomy, and less commonly used multiple subpial transections (Maehara 2001; Benifla 2006).

The ketogenic diet which contains high fat, low protein, and low carbohydrate has been used for drug-resistant epilepsy, particularly in children. While it has been found to be effective for many types of epilepsy, it is difficult to maintain over time, particularly in adults (Burakgazi 2016). However, modified versions of the ketogenic diet have been used in adults with refractory epilepsy (Kossoff 2008).

Neurostimulation devices have also been used as treatment for refractory epilepsy. The vagus nerve stimulator has been approved as adjunctive therapy for the treatment of adults and adolescents with refractory epilepsy (Milby 2009). It consists of a pacemaker-like/battery device implanted on the patient's upper chest, while the lead carries electrical stimulation to the left vagus nerve. Deep brain stimulation is an intracranial device, delivering electrical stimulation on a scheduled basis bilaterally to the anterior nucleus of the thalamus. A two-year follow-up of a randomised trial involving 100 patients showed a mean seizure reduction of 56%, while 14 patients were seizure-free for at least six months (Anderson 2008; Fisher 2010).

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

Epilepsy has numerous causes, which reflect underlying genetic or acquired brain dysfunction (Stafstrom 2015). The most recent ILAE classification of epileptic seizures defines focal, generalised, or unknown onset seizures, with subcategories of motor or nonmotor seizures with retained or impaired awareness (Fisher 2017).

A seizure is a paroxysmal alteration of neurologic function caused by the excessive, hyper-synchronous discharge of neurons in the brain (Stafstrom 2015). Epilepsy exists in a patient who has had a seizure and whose brain demonstrates a pathologic and enduring tendency to have recurrent seizures. Recently, the ILAE accepted recommendations to define epilepsy as a disease of the brain, defined by any of the following: (1) at least 2 unprovoked (or reflex) seizures occurring >24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (≥60%) after 2 unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher 2014).

Patients who are refractory to treatment experience comorbid illnesses, are at an increased risk of injury, premature death, psychological dysfunction and experience an overall reduced quality of life and as such account for most of the burden of epilepsy in the population (Laxer 2014; Chen 2018; Hogan 2018). Of the patients with drug-resistant epilepsy, many experience prolonged seizures or status epilepticus and, as a

result, suffer bodily injuries requiring hospitalisation. Other patients have shortened life spans because of the increased risk of sudden unexpected death that is associated with uncontrolled seizures. .

The risk of premature mortality is 1.6 to 3 times higher in people with epilepsy than in the general population (Thurman 2017). Mortality may be due to sudden unexpected death in epilepsy (SUDEP), fatal status epilepticus, an increased risk of death due to injuries such as drowning or falls, suicide, or nonpsychiatric comorbidities including neoplasia, cerebrovascular, and respiratory disease (Neligan 2011; Thurman 2017). The greater risk of death over the general population may be reduced by achieving seizure freedom through establishing effective treatment strategies (Neligan 2009; Neligan 2011; Mbizvo 2019).

Patients with refractory epilepsy account for the majority of disease burden of this neurological condition (Laxer 2014). Drug refractory epilepsy may be progressive, carrying risks of structural damage to the brain and nervous system. Consequently, patients experience comorbid illnesses, psychological dysfunction, and premature death (Laxer 2014; Chen 2018; Hogan 2018). In this regard, several studies have shown a higher risk of death in people who continued having seizures despite treatment when compared to people with epilepsy who are seizure free (Thurman 2017, Trinka 2013). Particularly, uncontrolled focal onset seizures are associated with increased mortality compared with mortality in patients with controlled seizures. Uncontrolled seizures also are a risk factor for suicide, SUDEP, accidents, and injuries (Mbizvo 2019; Liu 2020; Sander 2004; Epilepsy Society SUDEP). Adding to this burden is neuropsychiatric impairment caused by underlying epileptogenic processes, which seems to be independent of the effects of ongoing seizures themselves (Laxer 2014). For instance, refractory epilepsy can have a profound impact on people living with seizures or the fear of further seizures (Baker 1997; Kerr 2011; Jacoby 2008; Wheless 2006; Taylor 2011). Specifically, patients with drug refractory epilepsy experience significant limitations in their daily routines – simple activities such as driving, swimming, socializing or even taking a shower could pose the danger of unexpected seizure resulting in dire consequences. They also suffer significant social impairments that limit employment, reduce marriage rates, and decrease quality of life (French 2007; Laxer 2014). Collectively, these results indicate that achieving seizure freedom is critical to considerably improve the health status and quality of life of patients with drug-resistant epilepsy. Nevertheless, achieving seizure freedom is currently not the primary consideration in many clinical studies of epilepsy (Halford 2020).

Important co-morbidities:

People with epilepsy have a poorer overall health status, impaired intellectual and physical functioning, and a greater risk of accidents injuries, and suicide. They have a high rate of comorbidities, including somatic, behavioural, and psychiatric disorders (Neligan 2011; Stafstrom 2015). In patients with epilepsy, the prevalence of suicidal thoughts is 2–3 times higher than in those without epilepsy (Tellez-Zenteno 2007; Christensen 2007). Furthermore, suicide appears to be associated with chronic, drug resistant epilepsy (Mbizvo 2019).

Nonpsychiatric comorbidities include cardiovascular and respiratory disorders, diabetes, inflammation, obesity, headache, migraine, and arthritis (Stafstrom 2015). Several population studies have reported a higher prevalence of stroke, diabetes, heart disease, high blood pressure, asthma, chronic bronchitis, gastrointestinal ulcers, arthritis, thyroid conditions, migraine, Alzheimer's disease, and cancer in persons with a history of epilepsy (Boro 2003; Gaitatzis 2012).

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

A comprehensive battery of tests was conducted to assess the toxicological profile of oral cenobamate. Single and repeated dose toxicity studies were conducted in mice, rats and monkeys. The potential for carcinogenicity was studied in mice and rats, while reproductive and developmental toxicity was assessed in rats and rabbits. In vitro tests in bacteria and mammalian systems as well as in vivo tests in rats were used to investigate the genotoxic potential of cenobamate. As cenobamate is a central nervous system (CNS) acting drug, a series of studies were conducted to evaluate the cenobamate propensity for abuse potential in animal models of drug dependence. Finally, impurities in drug substance and drug product were evaluated in silico for potential general and genetic toxicity. All pivotal toxicity studies were conducted in full compliance with the Organisation for economic cooperation and development (OECD) good laboratory practice (GLP) guidelines. Rats and monkeys were chosen for pivotal toxicology studies because their pharmacokinetic (PK)/ toxicokinetic (TK) and metabolic profiles most closely matched those of humans.

The impurity profiles of cenobamate used in the pivotal non-clinical toxicology studies were consistent with cenobamate impurity profiles proposed for clinical use.

Key safety findings from toxicology studies with cenobamate are provided in the Table Part II.1.

Table Part II.1 - Key safety findings from non-clinical studies and relevance to human usage

Acute or repeat-dose toxicity studies	**Key findings:** Single-dose toxicity CNS effects of cenobamate have been linked to autonomic, behavioural and motor function. The CNS effects are dose-dependent and appear to be related to the C_{max}. The effects include ataxia, decreased activity and motor tone, and hypothermia. Mortality was observed at doses above the maximum tolerated dose. Median doses in mice and rats that resulted in impaired motor performance were much greater than those required to elicit antiepileptic effects in rodents. In rats, an oral no observed adverse effect level (NOAEL) following acute dosing could not be determined but is <30 mg/kg. The acute dose maximum tolerated dose (MTD) and NOAEL following intravenous (IV) administration were 50 mg/kg and 15 mg/kg, respectively. In Sprague-Dawley rats an oral acute dose NOAEL of <30 mg/kg corresponds to an estimated systemic exposure of less than 16.3 – 17.0 µg/mL. In Cynomolgus monkeys, no acute dose oral NOAEL could be determined, but the oral MTD and no observed effect level (NOEL) were found to be 160 mg/kg and 20 mg/kg, respectively. An oral acute NOEL of 20 mg/kg in Cynomolgus monkeys corresponds to an approximate systemic exposure of between 18 and 27 µg/mL, and an acute MTD of 160 mg/kg corresponds to a systemic exposure of more than 80 µg/mL. With regards to clinical exposures in patients, the 200 mg/day and 400 mg/day human doses produce steady state C_{max} values of 23.9 µg/mL and 45.5 µg/mL, respectively. However, the slow titration dosing regimen used in adult patients starts with a dose of 12.5 mg/day and increases slowly over 10 weeks to a target dose of 200 mg/day, and over 18 weeks to a maximum dose of 400 mg/day. Because of the clinical titration schedule patients will not initiate treatment with cenobamate at doses higher than 12.5 mg/day where exposures are well below rat and monkey acute toxicity NOELs. Repeat-dose toxicity The main findings involved CNS- and liver-related signs. **Effects on the Central Nervous System:** In the mouse morbidity and mortality were observed at doses ≥60 mg/kg/day. Morbidity was associated with CNS clinical signs including hypoactivity, lateral recumbency, cold to touch, and laboured/irregular respiration. The NOAEL in the mouse 13-week study was 30 mg/kg/day which corresponds to ~2.5 – 1.5-fold the human exposure (C_{max}) associated with the 200 and 400 mg doses.

	The most common finding in rats following repeated dosing for durations ranging from 28 days to 26 weeks was adverse clinical signs associated with the CNS. Morbidity and mortality were observed at high doses ≥48 mg/kg/day. Morbidity was associated with CNS clinical signs including uncoordinated gait, decreased activity, cold to touch, recumbency and slow skin turgor. Common findings at intermediate doses included reduced activity and ataxia; the incidence and severity increased with increasing dose. In the 26-week study, all findings resolved during the 8-week recovery period. The NOAEL in the rat 26-week study was 12 mg/kg which corresponds to exposure levels below (~0.2 – 0.7-fold) the human exposures (C_{max}) associated with the 200 and 400 mg doses. In rabbits, significant toxicity was noted at ≥50 mg/kg/day (Study 30/022). Treatment related effects included markedly reduced faecal output, body weight and food consumption, and CNS clinical signs including stiff and extended hindlimbs, subdued behaviour and prostration. In Cynomolgus monkeys, morbidity was observed at doses ≥27 mg/kg/day and was associated with clinical signs including tremor (whole body, limbs), apparent clonic convulsions, hypothermia, uncoordinated gait, hypoactivity and laboured respiration. Severe clinical signs (CNS-related) were noted after 3 days of treatment with 120 mg/kg/day (e.g. incoordination, severe hypoactivity, prostration, severe ataxia, horizontal nystagmus, hypothermia, absence of corneal reflex, absence of withdrawal reflex, labored respiration, tremors, tonic convulsions [clinical observations only], pallor of the gums, hypothermia and resulted in pre-terminal sacrifice). Subsequent 14-day studies revealed adverse CNS-related clinical signs at doses of ≥24 mg/kg/day. A 28-day study involving doses of 4, 12, and 36/24 mg/kg/day produced dose-dependent, CNS-related adverse clinical signs at ≥12 mg/kg/day. In the 52-week monkey study, adverse clinical signs (CNS-related) occurred at the highest dose of 27 mg/kg/day. When this dose was reduced to 22 mg/kg/day, the signs subsided. The NOAEL was determined to be 18 mg/kg/day (week 52 AUC_{0-24} of 1049 µg*h/mL for males and 542 µg*h/mL for females) which corresponds to exposure levels 0.8 – 2.6-fold the human exposures (C_{max}) associated with the 200 and 400 mg doses. The type and severity of these signs increased with increasing dose and resolved during the recovery periods. Following chronic exposure (26 weeks in rats and 52 weeks in monkeys), the NOAEL doses were very similar: 12 mg/kg/day in rats and 18 mg/kg/day in monkeys. However, these correspond to exposure levels below (~0.2 – 0.7-fold) the human exposures (C_{max}) associated with the 200 and 400 mg doses for the 12 mg/kg/day NOAEL in rats while the 18 mg/kg/day NOAEL in monkeys corresponds to exposure levels 0.8 – 2.6-fold the human exposures (C_{max}) associated with the 200 and 400 mg doses. The basis for these levels was adverse clinical signs in both species. Non-clinical pharmacology studies showed beneficial CNS effects of cenobamate and did not also result in obvious negative effects on the CNS. For example, in rotarod tests in mice and rats, the median neurotoxic dose was calculated to be between 50 and 350 mg/kg cenobamate, a dose greater than that required to elicit antiepileptic effects (i.e., 3-30 mg/kg). In an EEG study in cynomolgus monkeys, no evidence of drug-induced epileptic convulsions was observed at high doses that resulted in severe CNS toxicity. At the high dose where myoclonus and/or intention tremors were noted there was no evidence of seizure activity in 2 of 6 animals. There was no evidence of epileptic seizures at any time during the study. **Effects on the liver:** The target organ in the repeat-dose toxicity studies in mice was the liver and consisted of small increases in liver weight correlated microscopically to liver centrilobular hepatocyte hypertrophy. The NOAEL in the mouse 13-week study was 30 mg/kg/day which corresponds to ~2.5 – 1.5-fold the human exposure (C_{max}) associated with the 200 and 400 mg doses. The target organs from the repeat-dose toxicity studies in rats were the liver and the kidney. Dose related minimal to mild centrilobular hepatocellular hypertrophy, together with dose-related increases in liver weight, was observed in rats that received at least 24 mg/kg/day in the 26-week study, but this is considered to be an adaptive response and is not toxicologically relevant. The renal changes observed were only in males and associated with either male rat alpha 2U globulin mechanism or early chronic progressive nephropathy. Renal effects were considered toxicologically irrelevant as they have no counterpart in humans. The NOAEL in the rat 26-week study was 12 mg/kg which

	corresponds to exposure levels below (~0.2 – 0.7-fold) the human exposures (C_{max}) associated with the 200 and 400 mg doses. The target organ from the repeat toxicity study in monkeys was the liver. In the 52-week monkey study, increases in liver weights and microscopic hepatocellular hypertrophy occurred with dosages of 18 and 27/22 mg/kg/day. These changes were a non-adverse reversible response considered to be adaptive. In the high-dose animals, the liver changes resolved following a 3-month recovery period. The NOAEL in the 52-week study was 18 mg/kg/day which corresponds to exposure levels 0.8 – 2.6-fold the human exposures (C_{max}) associated with the 200 and 400 mg doses. **Relevance to human usage:** Non-clinical data reveal no special hazard for humans based on conventional repeated dose toxicity studies where the main findings were adverse CNS effects and adaptive hepatocellular hypertrophy. In the clinic, as in animals, CNS-related disorders are the most common treatment-related adverse events (AEs). Somnolence, abnormal coordination and headache are recognised as very common (≥1/10) adverse reactions and dysarthria, nystagmus, aphasia, and memory impairment are common (≥1/100 to <1/10) adverse reactions in the Ontozry SmPC. Hepatic enzyme increased is a common (≥1/100 to <1/10) adverse reaction in the Ontozry SmPC. In light of the above non-clinical findings, in the post-marketing period up to 20 November 2020, there were 125 somnolence (1 serious), 3 abnormal coordination, 67 headache (1 serious),11 dysarthria, 1 nystagmus, 4 aphasia (1 serious), 26 memory impairment, 1 hepatic function abnormal, 1 blood bilirubin decreased, 1 hepatic enzyme increased, and 1 liver function test increased spontaneous cases reported. These AEs are monitorable, are generally C_{max}-related, and may be minimized when dose levels are titrated over several weeks up to the efficacious dose (Module SVII.1).
Reproductive and developmental toxicity	**Key findings:** In a GLP fertility study in Sprague Dawley rats, there were no effects on estrous cycling; male or female fertility or mating indices; sperm motility, count, and morphology; or C-section parameters in Sprague Dawley rats given up to 44 mg/kg/day of cenobamate. In embryo-foetal development studies in rat and rabbit, maternal toxicity was observed at high doses. In the rat, the high dose of 60 mg/kg/day resulted in increased embryo-foetal mortality, reduced foetal body weights and incomplete foetal skeletal ossification, and this was associated with maternal toxicity. There was also a small increase in visceral malformations at this high dose. However, teratogenic potential could not be fully evaluated because of the high rate of embryo-foetal deaths, which resulted in an inadequate number of foetuses examined. Therefore, the embryo-foetal study in rats showed some possible teratogenic findings at the highest dose tested. 30 mg/kg/day was the NOEL for embryo-foetal toxicity which corresponds to maternal exposure levels likely lower than the clinical exposures with the 200 and 400 mg doses. There was no increase in malformations in rabbits when cenobamate was administered to pregnant rabbits. The NOEL for both maternal and embryo-foetal toxicity was 12 mg/kg/day which corresponds to maternal exposure levels well below (0.1 – 0.2-fold) clinical exposures with the 200 and 400 mg doses. In the pre- and post-natal development study in rat, neurobehavioral impairment (increased auditory startle response) was observed in the offspring at all doses. Female offspring from high dose dams showed reproductive effects (increased early resorptions and pre- and post-implantation loss; decreased numbers of corpora lutea, implantations and live foetuses). The NOAEL for both maternal and pre- and post-natal development was 22 mg/kg/day, which corresponds to exposure levels similar to clinical exposures with the 200 mg dose but below (~ 0.5-fold) clinical exposures with the 400 mg dose. According to the EMA post-approval commitment, a further study was performed to determine the embryo-foetal developmental toxicity and toxicokinetics, including the teratogenic potential, of cenobamate after twice daily administration to pregnant rats, in an effort to improve tolerability by decreasing C_{max} levels. Indeed, the previous study using the once daily oral dose, showed that tolerability was related to C_{max} levels. The vehicle, 0.5% (w/v) methylcellulose (400 cps) in deionized water, or cenobamate was administered to time-mated female CD® [Crl:CD®(SD)] rats twice daily (8 hours apart ±15 minutes) via oral gavage from Gestation Day (GD) 6 through 17. Following twice daily oral gavage administration of cenobamate to pregnant rats, C_{max} and $AUC_{0\text{-}24hr}$ values of cenobamate increased with increasing dose in an approximately dose-proportional manner on GD 6 and increased from 10 to 30 mg/kg/day in a less than dose-

	proportional manner with no increase from 30 to 50 mg/kg/day on GD 17. Systemic exposure (AUC_{0-24hr}) to cenobamate did not appear to change following repeated administration of cenobamate at 10 and 30 mg/kg/day, however, exposure decreased following repeated administration of cenobamate at 50 mg/kg/day. No cenobamate-related effects were observed on maternal survival at 10 to 30 mg/kg/day. One animal at 50 mg/kg/day was euthanized on GD 15. While the moribundity at 50 mg/kg/day was potentially cenobamate-related, all other animals (39 main study and 12 TK animals) at this dose survived to scheduled termination and therefore, not considered adverse. No cenobamate-related effects were observed on clinical findings, mean gestation body weights and body weight gain at 10 to 30 mg/kg/day or on mean gestation food consumption at 10 mg/kg/day. Non-adverse cenobamate-related findings included more frequently observed thin body condition and lower mean gestation body weights and body weight change at 50 mg/kg/day and lower mean gestation food consumption at 30 and 50 mg/kg/day. No cenobamate-related effects were observed on maternal macroscopic findings and on fetal sex ratios, body weights, or external, visceral, and skeletal examinations at any dose level evaluated. Based upon the lack of adverse findings, in this study the no-observed-adverse-effect level (NOAEL) for both maternal and embryo-fetal developmental toxicity was considered to be 50 mg/kg/day. Therefore, cenobamate did not show teratogenic potential up to 50 mg/kg/day when administered to female rats during gestation. **Relevance to human usage:** Adverse effects were seen in animals at exposure levels lower than clinical exposure levels and have possible relevance to clinical use. Reproductive/embryofoetal toxicity is an important potential risk (Module SVII.1.2).
Genotoxicity	**Key findings:** Cenobamate was negative for genotoxicity in in vitro (Ames, mouse lymphoma) and in vivo (rat bone marrow micronucleus) assays. **Relevance to human usage:** Not applicable
Carcinogenicity	**Key findings:** Oral administration of cenobamate to Tg.rasH2 mice for up to 26 weeks did not result in an increase in tumors. At Week 26, the plasma concentrations of cenobamate in male and female animals given 35 mg/kg/day were 59.5 µg/mL and 54.5 µg/mL, respectively. These exposure levels are slightly higher than the clinical exposure in patients at the maximum 400 mg/day dosage (C_{max} value of 45.5 µg/mL). Oral administration of cenobamate to male and female rats for up to 87 or 90 weeks, respectively, did not result in an increase in tumors. Plasma exposure at the highest dose tested in rats was less than that in humans at the maximum recommended human dose (MRHD) of 400 mg/day. **Relevance to human usage:** No carcinogenicity is expected.
Safety pharmacology	<u>Cardiovascular system, including potential effect on the QT interval</u> **Key findings:** *In vitro* tests on the cardiovascular system with sodium channels, rabbit Purkinje fibers, and human ether-à-go-go-related gene (hERG) showed some potential for effects including 1) shortened duration of the action potential and 2) lowering or depression of the plateau phase of action potential at ≥100 µM. However, cenobamate had no effects on cardiac (electrocardiogram [ECG]) or circulatory function as measured by telemetry in monkeys at single PO doses of 4, 12, and 36 mg/kg. Cenobamate was classified as low-risk hERG channel blocker with an IC_{50} of 1,869 µM. In addition, no evidence of cardiotoxicity was found in in vivo toxicity studies, including histopathologic evaluations of rats and monkeys. **Relevance to human usage:** In a thorough QT study in health volunteers (Study YKP3089C020), a dose dependent effect of QT shortening was noted at the recommended therapeutic dose of 200 mg/day (-10.8ms) and at a supratherapeutic dose of 500 mg/day dose (-18.4ms), that was not considered clinically concerning. QT shortening is considered an important potential risk (Module SVII.1.2). <u>Nervous system</u> **Key findings:** See summary under repeat-dose toxicity. <u>Respiratory system</u> **Key findings:** In the GLP rat respiratory study, the effect of cenobamate on respiratory function was assessed in conscious, freely moving rats by whole body plethysmography after oral administration at 10, 30, and 60 mg/kg.

	In this study cenobamate did not have any effect on respiratory rate, inspiratory time, expiratory time, relaxation time, tidal volume, peak inspiratory flow, peak expiratory flow and Penh (an index of bronchoconstriction status) in rats as compared with the vehicle-treated group. The only recorded effect was at the highest dose of 60 mg/kg, where a statistically significant decrease of the minute volume (volume of gas inhaled into the lungs per minute) throughout the recording period (about 20% at the maximum effect) was observed. **Relevance to human usage:** Cenobamate was not found to adversely affect the respiratory system in clinical trials. In the post-marketing period up to 20 November 2020, 7 spontaneous cases of dyspnoea (1 serious) were reported. This was the most frequently reported adverse reaction in the Respiratory, thoracic and mediastinal disorders system organ class (SOC). <u>Gastrointestinal system</u> **Key findings:** The effects of cenobamate on intestinal transit were examined in rats after a single dose and found that doses of both 30 and 60 mg/kg produced moderate, but statistically significant, delays in transit time compared to vehicle (-17 and -15%, respectively). **Relevance to human usage:** In the double-blind clinical trials, AEs of constipation were reported in a small subset of subjects (5.9%). Constipation, diarrhoea, nausea, vomiting and dry mouth are recognised adverse reactions with a frequency of common (≥ 1/100 to <1/10) in the Ontozry SmPC based on clinical trial data. In the post-marketing period up to 20 November 2020, there were 9 constipation, 11 diarrhoea, 35 nausea, 17 vomiting and 3 dry mouth spontaneous cases reported, none of which were serious.
Local tolerance	**Key findings:** No local tolerance studies were performed since the oral route is the intended method of administration in humans. **Relevance to human usage:** not applicable.
Other toxicity studies	<u>Juvenile toxicity</u> Cenobamate was administered using a dose escalation protocol to juvenile rats from PND 7 through PND 70, corresponding to the developmental period of newborn to young adult human ages. The toxicity pattern in juvenile rats was the same as that seen in adult rats, namely mortality and corresponding clinical signs at the highest exposure and absence of clinical signs at slightly lower doses/exposures. Effects on learning and memory occurred in treated male rats at the highest dose level, were related to direct exposure to cenobamate but were not a permanent effect. Target organ toxicity was the same in juvenile animals as in adults, i.e., non-adverse histopathologic changes to the liver and kidney which were reversible. The NOAEL was identified as the low dose (20/20/30/40 mg/kg/day in males and 15/15/20/20 mg/kg/day in females) based on mortality, clinical signs and decreased body weights/gains in the high and mid dose groups. Exposures at the NOAEL doses in the juveniles are consistent with the exposures observed at the NOAEL in the adult rat 26-week toxicity study. **Relevance for human usage:** Not relevant as the proposed indication is for adult patients. <u>Abuse liability</u> **Key findings:** Cenobamate did not produce robust effects indicative of physical dependence or withdrawal at doses up to 100 mg/kg/day which corresponds to approximately 1.6-fold the clinical exposure observed with the 200 mg dose but below (~ 0.8-fold) clinical exposures with the 400 mg dose. Cenobamate at ≤20 mg/kg did not show substitution for 3 mg/kg midazolam, while 60 and 180 mg/kg produced partial substitution at exposures 1.5-fold and 3.3-fold the clinical exposure with the 200 mg dose, and 0.8-fold and 1.8-fold the clinical exposure with the 400 mg dose. Cenobamate demonstrated a short-lived interoceptive stimulus state that was subjectively similar to chlordiazepoxide (CDP) (full generalisation) and d-amphetamine (partial generalisation) in male rats. There was no demonstrable behavioural index of similarity between cenobamate and morphine or the hallucinogen 2,5-Dimethoxy-4-Iodoamphetamine (DOI).

	Cenobamate produced minimal to no reinforcing behaviour in animals trained to self-administer midazolam. **Relevance for human usage:** Based on non-clinical data, cenobamate is expected to show low potential for drug abuse or dependence liability in humans. Clinical dependence studies have been conducted with cenobamate. The totality of the non-clinical and clinical data suggests that cenobamate has a low potential for abuse in human patients (see Module SVI). Other toxicology studies No additional immunotoxicity studies were conducted either with cenobamate as a review of non-clinical toxicology and drug disposition data did not suggest the need for specific immunotoxicity studies. Phototoxicity testing was not conducted because cenobamate does not absorb radiation at ultraviolet (UV)B, UVA or visible radiation wavelengths (290-700 nm) responsible for solar photosensitisation reactions.

Part II: Module SIII - Clinical trial exposure

Twenty-six clinical studies contribute to the safety evaluation of cenobamate. The studies included:

- Two adequate and well-controlled, double-blind (DB), placebo-controlled efficacy and safety studies (YKP3089C017 and YKP3089C013) with ongoing open-label extensions (OLE) in patients with partial onset seizures.
- One ongoing, open-label, safety and pharmacokinetic (PK) study (YKP3089C021) in patients with partial onset seizures.
- One Phase 2a, single-dose, pharmacodynamic (PD) proof-of-concept study in patients with photosensitive epilepsy (Study AA40616).
- Twenty-two Phase 1 studies in healthy volunteers and special populations.

For the 3 key studies, study identifiers starting with the substance code YKP3089 are abbreviated, i.e. YKP3089C013, YKP3089C017, and YKP3089C021 are shown as C013, C017, and C021 respectively.

Pooled data are presented for all Phase 2/3 studies: Studies C013, C017 and C021, herewith referred to as **Phase 2/3 pool**; as well as for the randomised, double-blind, period of studies C013 and C017, referred to as **Double-blind pool**. In addition, all the three studies (C013, C017 and C021) had an open-label period.

Overall a total of 2564 patients/subjects have been treated with cenobamate in the clinical trial programme (including patients who received placebo in the double-blind phase of a study who transitioned to cenobamate in the open-label phase).

- 607 healthy subjects treated with cenobamate (and an additional 125 subjects who received placebo).
- 12 patients in the Phase 2a study (who are included in the Phase 1 Pool data set).
- 442 patients treated with cenobamate in the double-blind phase of controlled clinical trials; additionally, 163 of the 216 patients who received placebo in the double-blind phase of a clinical trial transitioned to cenobamate in the open-label extension phase.
- 1340 patients treated with cenobamate in the open-label safety study (C021).

Durations of exposure for the Phase 2/3 pool and for the double-blind pool are presented in Table Part II.2 and Table Part II.3, respectively. Durations of exposure by age group and gender for the Phase 2/3 pool and for the double-blind pool are presented in Table Part II.4 and Table Part II.5, respectively. Duration of exposures by dose for the Phase 2/3 pool and for the double-blind pool are presented in Table Part II.6 and Table Part II.7, respectively. Duration of exposures by race are presented for the Phase 2/3 pool and for the double-blind pool in Table Part II.8 and Table Part II.9, respectively.

Table Part II.2 - Duration of Cenobamate Exposure - All Phase 2/3 Pool

Duration of exposure	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]
< 30 days	99 (5.1)	4.02
30 to < 90 days	127 (6.5)	19.57
90 to < 180 days	117 (6.0)	39.86
180 to < 365 days	146 (7.5)	104.71
365 to < 540 days	87 (4.5)	104.34
540 to < 720 days	63 (3.2)	108.08
720 to < 1080 days	584 (30.0)	1594.92
1080 to < 1440 days	418 (21.5)	1341.99
1440 to < 1800 days	8 (0.4)	34.67
≥ 1800 days	296 (15.2)	1840.01
Total	1945 (100.0)	5192.18

[1]Percentages are based on the overall N = 1945 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of June 01, 2020. Source: Data Package 3 Table SIII.1.1

Table Part II.3 - Duration of Cenobamate Exposure - Double-blind Pool

Duration of exposure	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]	Placebo Patients n (%)[1]	Cumulative person time (person-years)[2]
< 30 days	23 (5.2)	0.93	6 (2.8)	0.23
30 to < 90 days	70 (15.8)	13.00	40 (18.5)	8.36
90 to < 180 days	349 (79.0)	113.91	170 (78.7)	52.19
180 to < 365 days	0 (0.0)	0	0 (0.0)	0
365 to < 540 days	0 (0.0)	0	0 (0.0)	0
540 to < 720 days	0 (0.0)	0	0 (0.0)	0
720 to < 1080 days	0 (0.0)	0	0 (0.0)	0
1080 to < 1440 days	0 (0.0)	0	0 (0.0)	0
1440 to < 1800 days	0 (0.0)	0	0 (0.0)	0
≥ 1800 days	0 (0.0)	0	0 (0.0)	0
Total	442 (100.0)	127.83	216 (100.0)	60.79

[1]Percentages for active group are based on the overall N = 442 used as denominator, and percentages for placebo group are based on the overall N = 216 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of July 01, 2019. Source: Data Package 3 Table SIII.1.2

Table Part II.4 - Duration of Cenobamate Exposure by Age Group and Gender - All Phase 2/3 Pool

Age Group Categories	Cenobamate Patients n (%)[1]		Cumulative person time (person-years)[2]	
	Male	Female	Male	Female
Adolescents (<18 years)	0 (0.0)	0 (0.0)	0.0	0.0
Adults (18 to 39 years)	548 (28.2)	482 (24.8)	1526.41	1240.82
Adults (40 to 64 years)	405 (20.8)	459 (23.6)	1157.41	1133.95
Adults (≥65 years)[3]	24 (1.2)	27 (1.4)	58.83	74.76
Total	977 (50.2)	968 (49.8)	2742.65	2449.53

[1]Percentages are based on the overall N = 1945 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
[3]Based on age at time of study entry.

Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of June 01, 2020. Source: Data Package 3 Table SIII.2.1

Table Part II.5 - Duration of Cenobamate Exposure by Age Group and Gender - Double-blind Pool

Age Group Categories	Cenobamate Patients n (%)[1]		Cumulative person time (person-years)[2]		Placebo Patients n (%)[1]		Cumulative person time (person-years)[2]	
	Male	Female	Male	Female	Male	Female	Male	Female
Adolescents (<18 years)	0(0.0)	0 (0.0)	0.0	0.0	0 (0.0)	0 (0.0)	0.0	0.0
Adults (18 to 39 years)	126(28.5)	114 (25.8)	37.97	32.04	68 (31.5)	50 (23.1)	19.49	14.48
Adults (40 to 64 years)	91 (20.6)	105 (23.8)	26.69	29.07	43 (19.9)	51 (23.6)	11.68	13.71
Adults (≥65 years)[3]	1 (0.2)	5 (1.1)	0.33	1.72	4 (1.9)	0 (0.0)	1.43	0.0
Total	218 (49.3)	224 (50.7)	64.99	62.83	115 (53.2)	101 (46.8)	32.60	28.19

[1]Percentages for active group are based on the overall N = 442 used as denominator, and percentages for placebo group are based on the overall N = 216 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
[3]Based on age at time of study entry
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of July 01, 2019. Source: Data Package 3 Table SIII.2.2

Table Part II.6 - Duration of Cenobamate Exposure by Dose - All Phase 2/3 Pool

Exposure Levels (mg)	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]
12.5	1336 (68.7%)	51.65
25	1271 (65.3%)	49.04
30	1 (0.1%)	0.25
50	1684 (86.6%)	169.31
75	6 (0.3%)	1.80
100	1787 (91.9%)	467.64
125	2 (0.1%)	0.97
150	1572 (80.8%)	467.72
199	1 (0.1%)	0.26
200	1619 (83.2%)	1620.66
225	3 (0.2%)	0.40
250	835 (42.9%)	545.71
275	1 (0.1%)	0.25
300	871 (44.8%)	896.29
325	1 (0.1%)	1.33
350	424 (21.8%)	327.77
375	1 (0.1%)	0.91
400	386 (19.8%)	519.46
450	1 (0.1%)	0.08
500	1 (0.1%)	0.00
600	2 (0.1%)	0.01
700	1 (0.1%)	0.00
800	1 (0.1%)	0.02

[1]Percentages are based on the overall N = 1945 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of June 01, 2020. Source: Data Package 3 Table SIII.3.1

Table Part II.7 - Duration of Cenobamate Exposure by Dose - Double-blind Pool

Exposure Levels (mg)	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]
12.5	0 (0.0)	0.0
25	0 (0.0)	0.0
50	407 (92.1)	14.71
75	0 (0.0)	0.0
100	433 (98.0)	43.23
125	0 (0.0)	0.0
150	293 (66.3)	17.30
200	282 (63.8)	35.16
225	0 (0.0)	0.0
250	3 (0.7)	0.35
275	0 (0.0)	0.0
300	84 (19.0)	4.75
350	2 (0.5)	0.53
400	71 (16.1)	11.61
500	0 (0.0)	0.0

[1]Percentages for active group are based on the overall N = 442 used as denominator.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of July 01, 2019. Source: Data Package 3 Table SIII.3.2

Table Part II.8 - Duration of Cenobamate Exposure by Race - All Phase 2/3 Pool

Race Group Categories	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]
American Indian or Alaska Native	PPD (3.0)	137.18
Asian	PPD (9.3)	484.38
Black or African American	PPD (3.3)	153.72
Native Hawaiian or Other Pacific Islander	PPD (0.3)	12.04
Other	PPD (5.3)	232.55
Unknown	PPD (0.3)	26.01
White	PPD (78.5)	4146.31
Total	PPD (100.0)	5192.18

[1]PPD.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of June 01, 2020. Source: Data Package 3 Table SIII.4.1

Table Part II.9 - Duration of Cenobamate Exposure by Race - Double-blind Pool

Race Group Categories	Cenobamate Patients n (%)[1]	Cumulative person time (person-years)[2]	Placebo Patients n (%)[1]	Cumulative person time (person-years)[2]
American Indian or Alaska Native	0 (0.0)	0.0	0 (0.0)	0.0
Asian	PPD (18.3)	20.87	PPD (25.0)	13.87

Black or African American	PPD (2.5)	2.81	PPD (2.8)	1.90
Native Hawaiian or Other Pacific Islander	0 (0.0)	0.0	0 (0.0)	0.0
Other	PPD (2.5)	2.94	PPD (1.9)	0.99
Unknown	PPD (0.7)	0.71	PPD (0.9)	0.48
White	PPD (76.0)	100.50	PPD (69.4)	43.54
Total	PPD (100.0)	127.83	PPD (100.0)	60.79

[1]PPD.
[2]Person time in number of years is calculated as the number on days the subjects were on treatment divided by 365.25.
Exposure summary is based on pre-specified exposure data derived in the ADaM datasets (ADEX)
Data cut as of July 01, 2019. Source: Data Package 3 Table SIII.4.2

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

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

Important exclusion criteria[1] were:

1. History of serious systemic disease, including hepatic insufficiency, renal insufficiency, a malignant neoplasm, any disorder in which prognosis for survival is less than 3 months, or any disorder which in the judgment of the investigator will place the subject at excessive risk by participation in a controlled trial

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: A dedicated Phase 1 PK study (Study YKP3089C027) explored the effects of cenobamate in hepatic impairment, while Study YKP3089C028 characterised the PK in patients with renal impairment. Recommendations regarding the treatment and dosing of patients with hepatic and renal impairment are provided in the Ontozry SmPC.

2. A history of nonepileptic or psychogenic seizures

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale: Cenobamate is not indicated for use in these types of seizures**.**

3. Primary generalized epilepsies

Reason for exclusion: The development program was focused on focal-onset seizures in epilepsy.

Is it considered to be included as missing information? No

Rationale: Cenobamate is not indicated for primary generalized epilepsies.

4. History of seizure clusters (episodes lasting less than 30 minutes in which multiple seizures occur with such frequency that the initiation and completion of each individual seizure cannot be distinguished) within 3 months prior to Visit 1

Reason for exclusion: Inability of patients with cluster seizure to participate in a clinical trial. To avoid confounding factors affecting efficacy assessments.

Is it considered to be included as missing information? No

Rationale: Cluster seizures represent the potential for a severe acute medical condition. Cenobamate is not indicated for acute treatment in acute seizures or status epilepticus.

[1] Based on Studies 017 and 013

5. Presence or previous history of Lennox-Gastaut syndrome

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and to avoid the use of placebo in this high-risk patient population.

Is it considered to be included as missing information? No

Rationale: Cenobamate is not indicated for use in Lennox-Gastaut syndrome.

6. Scheduled epilepsy surgery within 8 months after Visit 1

Reason for exclusion: This requirement was to avoid confounding factors on efficacy assessment, and to ensure that patients were not lost to follow up.

Is it considered to be included as missing information? No

Rationale: The exclusion criterion does not refer to a specific clinical condition or disease severity, rather it refers to the expected ability of the patients to conclude the study. No relevant clinical differences are expected in this population.

7. Pregnancy or lactation

Reason for exclusion: Pregnant and lactating women are routinely excluded from Phase 2/3 clinical trials.

Is it considered to be included as missing information? No

Rationale: Reproductive/embryofoetal toxicity is an important potential risk of cenobamate (Module SVII.1.2) as non-clinical studies in the rat have shown embryofoetal mortality, neurobehavioural effects and impairment in offspring (Module SII).

8. Any clinically significant laboratory abnormality that in the opinion of the investigator would exclude the subject from the study; Liver transaminases (AST or ALT) above twice the upper limit of normal or total or direct bilirubin not within normal limits

Reason for exclusion: This broad exclusion criterion was to avoid confounding factors related to safety and efficacy assessments.

Is it considered to be included as missing information? No

Rationale: Information regarding renal and hepatic impairment was collected via Phase 1 studies. Assessments are also available from Study 021. Recommendations regarding the treatment and dosing of patients with hepatic and renal impairment are provided in the Ontozry SmPC.

10. An active CNS infection, demyelinating disease, degenerative neurologic disease, or any CNS disease deemed to be progressive during the course of the study that may confound the interpretation of the study results

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and patient safety. Baseline to endpoint measurements are confounded in progressive diseases.

Is it considered to be included as missing information? No

Rationale: The exclusion criteria do not refer to a specific clinical condition or disease severity, rather they refer to the expected ability of the patients to conclude the study. No relevant clinical differences are expected in this population.

11. Any clinically significant psychiatric illness, psychological, or behavioral problems that, in the opinion of the investigator, would interfere with the subject's ability to participate in the study; Presence of psychotic disorders and/or unstable recurrent affective disorders evident by use of antipsychotics; presence or recent history (within 6 months) of major depressive episode

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and patient safety. To ensure the ability to conclude the study.

Is it considered to be included as missing information? No

Rationale: No relevant clinical differences are expected in this population in terms of treatment of epilepsy.

13. History of alcoholism, drug abuse, or drug addiction within the past 2 years

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: No clinically significant pharmacokinetic differences were observed for either cenobamate or alcohol when administered concomitantly. The Ontozry SmPC provides guidance for concomitant use of cenobamate with CNS depressants, including alcohol.

15. Current use of phenytoin, phenobarbital, or metabolites of these drugs, intermittent rescue benzodiazepines >1 time/month (within 1 month of Visit 1)

Reason for exclusion: The coadministration of cenobamate increased phenobarbital and phenytoin plasma exposures (AUC) by approximately 37% and 84%, respectively. Dose adjustments are to be considered when phenobarbital and phenytoin are co-administered with cenobamate. The need for dose adjustments would have compromised the blinding of the studies. These products were thus excluded for the avoidance of confounding factors.

Rescue benzodiazepines would have indicated that the patients background AED regimen is not stable, changes in medication could impact the efficacy analysis. The need for intermittent benzodiazepines would confound the results and would impact the efficacy analysis (i.e. seizure frequency).

Is it considered to be included as missing information? No

Rationale: The interactions between cenobamate and phenytoin or phenobarbital were investigated in Study C021.

Patients taking benzodiazepines were included in the clinical program. The exclusion criteria do not refer to a specific clinical condition or disease severity. No relevant clinical differences are expected in this population. The ONTOZRY SmPC provides guidance for dose adjustments needed in case of concomitant use of phenobarbital/phenytoin with cenobamate as clinically relevant (Module SVII.1.1).

18. History of status epilepticus within 3 months of Visit 1

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and to avoid the use of placebo in this high-risk patient population.

Is it considered to be included as missing information? No

Rationale: Cenobamate is not indicated for use in status epilepticus.

19. History of 1 serious drug-induced hypersensitivity reaction (including but not limited to Stevens Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) or any drug-related rash requiring hospitalization

Reason for exclusion: Patients with a history of serious drug-induced hypersensitivity reaction may have been more susceptible for DRESS and hypersensitivity, known risks of cenobamate.

Is it considered to be included as missing information? No

Rationale: Drug rash with eosinophilia and systemic symptoms (DRESS) is an important identified risk and hypersensitivity is an important potential risk (Module SVII.1.2).

20. History of AED-associated rash that involved conjunctiva or mucosae or more than one maculopapular rash that required discontinuation

Reason for exclusion: Patients with a history of AED-associated rash may be more susceptible for drug-induced skin reactions, including rash, which is a known adverse drug reaction (ADR) of cenobamate.

Is it considered to be included as missing information? No

Rationale: Skin reactions are recognised as an identified risk of cenobamate (Module SVII.1.1).

21. Patients with renal insufficiency

Reason for exclusion: To avoid confounding factors affecting safety and efficacy assessments and patient safety.

Is it considered to be included as missing information? No

Rationale: In subjects with mild or moderate renal impairment, cenobamate plasma exposure (AUC) increased 1.4- to 1.5-fold following a single dose of cenobamate 200 mg. In subjects with severe renal impairment receiving a single cenobamate dose of 100 mg, exposure was comparable to that of healthy controls after correcting for differences in dose. A retrospective analysis of subjects included in the PopPK analysis identified 215 subjects with mild renal impairment (GFR=60 go <90 mL/min), and 17 subjects with moderate renal impairment (GFR=30 to <60 mL/min) based on creatinine clearance estimates. No patients with focal onset seizures and severe renal impairment (GFR<30 mL/min) were included in the popPK analysis. The popPK model predicted the PK of the broader population of subjects with renal impairment well without a covariate for renal function, indicating that the PK cenobamate in subjects with renal impairment is not substantially different from subjects with normal renal function.

As described in the Ontozry SmPC, cenobamate should be used with caution and dose reduction may be considered in patients with mild to moderate (creatinine clearance 30 to <90 ml/min) or severe (creatinine clearance <30 ml/min) renal impairment. The maximum recommended dose in patients with mild, moderate,

or severe renal impairment is 300 mg/day. Cenobamate should not be used in patients with end-stage renal disease or patients undergoing haemodialysis.

22. Absolute neutrophil count less than 1500/µL

Reason for exclusion: To avoid confounding factors in the safety analysis; represents a patient population too ill to participate in clinical study.

Is it considered to be included as missing information? No

Rationale: Haematological parameters were followed in the clinical program, no clinically meaningful signals were seen neither in the double-blind phase, nor in the open-label extension phase of the clinical development programme.

23. Clinical or ECG evidence of serious cardiac disease, including ischemic heart disease, uncontrolled heart failure, and major arrhythmias, or relevant replicated changes in QT intervals (QTcF less than 340 msec or greater than 450 msec in males and greater than 470 msec in females); Presence of congenital short QT syndrome

Reason for exclusion: Patient safety in clinical development, confounding safety analysis.

Is it considered to be included as missing information? No

Rationale: The results of the thorough QT study (Study YKP3089C020) demonstrated that cenobamate doses up to 500 mg/day does not induce a dose-dependent prolongation of the QTc and cenobamate did not cause a clinically meaningful effect on cardiac conduction (i.e., the PR and QRS intervals). There was QT shortening at the recommended 200 mg/day dose (-10.8ms) and at higher than the clinically recommended dose of 500 mg/day dose (-18.4ms). Information is included in the Ontozry SmPC providing guidance for treating physicians. QT shortening is an important potential risk (Module SVII.1).

24. Platelet counts lower than 80,000/µL in subjects treated with valproate (VPA)

Reason for exclusion: VPA is associated with thrombocytopenia (Buoli 2018). Patients needed to be stable medically and in terms of dose of VPA to avoid confounding of the safety assessments.

Is it considered to be included as missing information? No

Rationale: Cenobamate is not associated with reduced platelet counts or thrombocytopenia, no clinically meaningful signals were seen either in the double-blind phase, or in the open-label extension phase of the clinical development programme. Only 1 case of platelet count decreased (serious) was reported in the post-marketing period up to 20 November 2020, in a patient with medical history of respiratory distress syndrome and on several concomitant medications ([PPD]). The event resolved, follow up information has been requested.

25. Suicidal attempt or ideation

Reason for exclusion: To avoid confounding factors in safety analysis.

Is it considered to be included as missing information? No

Rationale: Higher rates of suicidality and suicidal ideation are reported in patients with epilepsy, as well as with anti-epileptic medicinal products in several indications. Suicidality is included as an important potential risk (class effect) (Module SVII.1.2).

28. Current use of any of the following medications: clopidogrel, fluvoxamine, amitriptyline, clomipramine, methadone, ifosfamide, cyclophosphamide, efavirenz

Reason for exclusion: To avoid confounding factors due to the potential for interactions. Cenobamate is extensively metabolised. The primary metabolic pathway is glucuronidation via UGT2B7 and to a lesser extent by UGT2B4. Minor pathways for metabolism of cenobamate include oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.

Is it considered to be included as missing information? No

Rationale: Interactions have been fully characterised and described in the Ontozry SmPC along with dose adjustment recommendations.

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 (≥1/10,000 to <1/1,000), adverse reactions with a long latency, or those caused by cumulative exposure.

As of 01 June 2020, a total of 2564 patients/subjects have been exposed to at least 1 dose of cenobamate in the clinical development program. It should be noted, that the safety data pool for cenobamate includes also open-label extension data from the Studies 013, 017 and 021.

In the Double-blind pool 349 patients (79.0%) were exposed to cenobamate for 90 to <180 days (Table Part II.3). However, in the All Phase 2/3 pool, 66.9% of the patients were exposed to cenobamate for ≥720 days (Table Part II.4). The long duration of exposure to cenobamate provides evidence for a favourable safety and tolerability profile for the drug.

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

Table Part II.10 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant and breastfeeding women: Female subjects who were pregnant or lactating were excluded from enrolling in the cenobamate

Breastfeeding women	clinical studies. There are no adequate data on the developmental risk associated with the use of cenobamate in pregnant women. A total of 19 cenobamate-treated patients/subjects had 20 pregnancies reported across the clinical development programme. During the post-marketing period there were 5 pregnancy cases reported up to 20 November 2020. Further details of the pregnancy cases are provided in Module SVII.1.2. There are no data available on the presence of cenobamate in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. No cases relating to lactation were reported in the post-marketing setting up to 20 November 2020. Reproductive/embryofoetal toxicity is an important potential risk (Module SVII.1.2), based on the non-clinical findings (Module SII).
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Patients with hepatic impairment: Cenobamate plasma AUC was 1.9-fold and 2.3-fold higher in subjects with mild and moderate hepatic impairment, respectively, following a single oral 200 mg dose of Cenobamate compared to matched healthy controls. The effect of severe hepatic impairment on cenobamate pharmacokinetics has not been studied. Patients with renal impairment: Cenobamate plasma AUC was 1.4-fold to 1.5-fold higher in subjects with mild (CLcr 60 to < 90 mL/min) and moderate (CLcr 30 to < 60 mL/min) following a single oral 200 mg dose of Cenobamate compared to healthy controls. In subjects with severe (CLcr < 30 mL/min) renal impairment, cenobamate plasma AUC did not change significantly compared to healthy controls following single oral 100 mg dose of Cenobamate. The effect of haemodialysis on cenobamate pharmacokinetics has not been studied. Patients with cardiovascular impairment: In a placebo-controlled QT study in healthy volunteers, dose-dependent shortening of the QTcF interval has been observed with Cenobamate. The mean ΔΔQTc is -10.8 [-13.4, -8.2] msec for 200 mg once daily and -18.4 [-21.5, -15.2] msec for 500 mg once daily (1.25 times the maximum recommended dosage). Reductions below 340 msec were not observed. Immunocompromised patients: with the exception of patients with the human immunodeficiency virus, the clinical development program did not generally exclude immunocompromised patients otherwise meeting the inclusion/exclusion criteria (see Module SIV.1). Patients with a disease severity different from inclusion criteria in clinical trials: Cenobamate is indicated for the adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products. Cenobamate is not indicated for use as monotherapy.

Population with relevant different ethnic origin	Duration of exposure by race is provided in Module SIII. The majority of patients treated with cenobamate were White (78.5%) followed by Asian (9.3%), Other (5.3%), Black or African American (3.3%), American Indian or Alaska Native (3.0%), Native Hawaiian or Other Pacific Islander (0.3%), and Unknown (0.3%) in the Phase 2/3 pool (Table 9). A similar pattern was observed in the double-blind pool with the majority of patients were White (76.0%) followed by Asian (18.3%), Other (2.5%), Black or African American (2.5%), and Unknown (0.7%) (Table 10). There were no patients of American Indian or Alaska Native or Native Hawaiian or Other Pacific Islander in the double-blind pool. No clinically significant effect of ethnicity on the pharmacokinetics of Ontozry was noted in a population PK analysis of pooled data from clincial studies from subjects categorised as Asian, Black, Caucasian, Hispanic, or Other.
Other	Patients using oral contraceptives: Due to a risk of decrease in plasma concentration of CYP3A4 metabolised medicines, women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Cenobamate was licensed for use in the USA on 21 November 2019, under the invented name XCOPRI®. Subsequently, it was placed on the US market in late May 2020.

Cenobamate was also approved in the EU and launched in June 2021.

SV.1.1 Method used to calculate exposure

The method used to calculate the cumulative yearly exposure of patients is based on the grams of medicinal product sold divided the DDD (0.2 g, WHO Collaborating Centre), divided the period of 1 year (365.25 days)

SV.1.2 Exposure

According to the PSUR of cenobamate dated 27NOV2023, 11,513,657 tablets (corresponding to 1,319,783 g) of cenobamate have been sold from the first launch of cenobamate (JUN2021) in Europe.

Considering the DDD of 0.2 g, it can be conservatively estimate that in the cumulative period 18,066 patients were annually exposed to cenobamate (1,319,783 g / 0.2 g / 365.25 days).

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

Potential for misuse for illegal purposes

To assess the potential for abuse associated with the administration of cenobamate, a Drug Abuse Potential Assessment was conducted for cenobamate (DAPA, 2018). To identify clinical evidence of abuse potential, a systematic review of AE terms potentially related to abuse, subjective effects, and other psychiatric or nervous system effects was conducted for 24 of the 26 cenobamate clinical studies. One study was specifically designed to assess abuse potential (Study YKP3089C024, Oral abuse potential in non-dependent recreational drug users with sedative experience).

Based on the evaluation of the primary and secondary measures in the Human Abuse Liability study (Study YKP3089C024), both doses (200 mg/day and 400 mg/day) of cenobamate showed an abuse potential profile that was significantly lower compared to alprazolam in a population of recreational sedative users (Module 2.7.2, Section 2.5.3). The lower dose of cenobamate (200 mg/day) was similar to placebo on the primary measure (peak drug liking) and on the key secondary measure of “Take Drug Again”. Although cenobamate 400 mg/day did differentiate from placebo on the primary and key secondary measures related to abuse potential, this study demonstrated that even with dose escalation, cenobamate 400 mg/day showed significantly decreased peak effects even when compared to the lowest dose of alprazolam (1.5 mg) on the majority of primary and key secondary measures (Module 2.7.2, Section 3.5.1).

Overall, the non-clinical data indicate that cenobamate shows minimal reinforcing effects, shares dose-dependent discriminative stimulus effects with benzodiazepines, and has significant behavioral and motor-impairing effects at exposure levels exceeding that anticipated clinically (Module 5.3.5.3, Drug Abuse Potential Assessment, Section 3.2). Results of the physical dependence studies indicate that cenobamate has a low potential for physical dependence when administered for 14 days at doses up to 100 mg/kg (equivalent to approximately 1.6-fold the mean steady-state exposure observed with 200 mg/day in humans, but lower than steady-state exposure in humans at 400 mg/day), as shown by minimal and sporadic changes in behaviour and clinical signs upon abrupt cessation of treatment.

In all clinical studies of cenobamate, there were no reports of misuse, abuse, or diversion (Module 5.3.5.3, ISS, Section 13.2). The most consistently reported potentially abuse-related AEs in healthy subjects were somnolence and dizziness, with both events occurring at a higher incidence compared with placebo and increasing with increasing dose of cenobamate. There were no events of dizziness (which is not in itself a signal of abuse potential) that were associated with feelings of giddiness.

Clinical adverse event data in that study suggest that the potential euphoric and sedative effects associated with cenobamate are less than those of a benzodiazepine (Module 2.7.2 Section 2.5.3). Importantly, there were no reports of euphoric or elevated mood, feeling drunk, or feeling abnormal in healthy subjects and patients with epilepsy following single dose administration of cenobamate up to 750 mg.

In Study C024, the rate of euphoric mood AEs in the cenobamate 400 mg arm was similar to that observed with alprazolam 1.5 mg and 3.0 mg arms, but no instances of euphoric mood were observed in the cenobamate 200 mg arm. The overall incidence of euphoric mood in patients (0.3%) is comparable to that reported for the unscheduled AED, eslicarbazepine (0.1-1%, Zebinix SmPC).

Seven (0.3%) patients experienced euphoric mood in the Phase 2/3 pool and all events occurred at doses <400 mg. None of these patients had AEs associated with suicidal thoughts.

Overall, the occurrence of potentially abuse-related adverse events was low with the exception of somnolence and dizziness. The occurrence of such events should consider that patients are taking other concomitant medications, which could contribute to the observation of such potentially abuse-related adverse events and that these reported events could in part be related to the underlying condition of

epilepsy. In addition, the profile of potentially abuse-related adverse events for cenobamate in patients is similar to that reported for eslicarbazepine (Zebinex SmPC; Clinical Safety Review for NDA 022-416).

In the post-marketing period up to 20 November 2020, there was only 1 case of euphoric mood (non-serious) reported.

In summary, the analysis of abuse-related data from human studies of cenobamate indicates that the abuse and dependence potential of cenobamate is low and similar to eslicarbazepine, which is not a controlled substance and not subject to significant abuse in the community.

At the request of the FDA the XCOPRI® prescribing information presents cenobamate as a controlled substance (Schedule V). The risk of potential abuse and dependence is discussed further in Module SVII.1.1.

Part II: Module SVII - Identified and potential risks

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

Cenobamate was seeking marketing authorisation for adjunctive treatment of focal-onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic medicinal products. Patients with treatment-resistant epilepsy have increased rates of mortality and morbidity associated with recurrent seizures and very limited likelihood to obtain seizure freedom with currently available treatment options. In clinical trials, cenobamate has demonstrated a unique, positive benefit-risk profile as adjunctive therapy for patients who do not respond to currently available therapy. Cenobamate sholud be administered in combination with other anti-epileptic products. There are more than 15 anti-epileptic medicines available in the EU (counted by INN), many of which share a well-recognised adverse reaction profile consistent with what is seen with cenobamate.

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:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Constipation
- Diarrhoea
- Nausea
- Vomiting
- Dry Mouth
- Fatigue
- Hypersomnia
- Nystagmus
- Hepatic enzymes elevated

The primary adverse drug reactions for cenobamate are common across the class of anti-epileptic drugs, and include common reactions such as **somnolence, dizziness, fatigue, headache, abnormal coordination and abnormal movements, visual and cognitive disturbances, irritability and gastrointestinal effects**. In the cenobamate clinical development programme, most of these were mild to moderate in severity, occur early in treatment and diminish in frequency as patients progress with treatment.

Further, most adverse reactions seen with cenobamate were dose dependent, and could be managed through a slow titration within a therapeutic dose range to tolerability and clinical effect. It is expected that most of the adverse drug reactions seen with cenobamate will be very well known in medical management of patients with epilepsy.

While there is potential impact to function or activities of daily living from a number of these reactions such as dizziness, sedation, visual and cognitive impairment, and abnormal movements, it should be noted that uncontrolled epilepsy itself carries very high risks for these same activities, and the management of activities where impaired consciousness or motor function might pose a risk (such as driving) is embedded in current medical practice for the treatment of epilepsy.

The **increase in hepatic enzymes** is also expected with AEDs or many other medicinal products, which are extensively metabolised. There were reported AEs of increased liver enzymes in the double-blind pooled

database for ALT (1.6% cenobamate, 0 placebo) and AST (1.4% cenobamate, 0.5% placebo). Biochemical liver parameters were somewhat increased at the end of titration (ALT: 2.7 U/L cenobamate, -0.2 placebo; AST 1.4 U/L cenobamate, 0.1 placebo) but showed no mean increase at the end of the double-blind period (ALT: -0.5 U/L cenobamate, -0.3 placebo; AST: -0.3 U/L cenobamate, 0.0 UL placebo). Alanine aminotransferase increases of ≥3 ULN occurred in 1.4% of cenobamate patients, and AST increases of ≥3 ULN occurred in 0.5%; no placebo patients had AST or ALT values ≥3 ULN.

No patient had bilirubin values ≥2 ULN. Hence, there were no patients fulfilling the search criteria for potential Hy's law cases (ALT/AST values >3 ULN, bilirubin >2 ULN, ALKP <2 ULN) (MAA 2.7.4 Table 113, Table 114)

The Ontozry SmPC includes information regarding dosing and treatment of hepatically impaired patients as the PK in this subpopulation has been characterised in Phase I study.

In the post-marketing period up to 20 November 2020, there were 1 hepatic function abnormal, 1 hepatic pain, 1 blood bilirubin decreased, 1 hepatic enzyme increased, and 1 liver function test increased spontaneous cases reported. None of these cases were serious.

Possible increases in hepatic enzymes are well-known to health professionals, across therapeutic classes of medications, and do not require additional pharmacovigilance activities or additional risk minimisation measures.

Gastrointestinal reactions (such as constipation, diarrhoea, dry mouth) are not of significant clinical relevance to be considered to be associated with additional risk and therefore are classified as important risks in the risk management plan.

In the post-marketing period up to 20 November 2020, there were 9 constipation, 11 diarrhoea, 35 nausea, 17 vomiting and 3 dry mouth spontaneous cases reported, none of which were serious.

The above listed reactions have relatively low clinical impact on patients, in light of the treated indication, and are not considered important risks of cenobamate.

Known risks that do not impact the risk-benefit profile:

- Somnolence
- Dizziness
- Vision blurred
- Confusional state
- Ataxia
- Irritability
- Dysarthria
- Aphasia
- Memory impairment
- Diplopia
- Headache

The above listed ADRs are to be expected in epileptic patients treated with several concomitant AEDs. Based on the guidance in the Ontozry SmPC and the experience existing so far with a number of AEDs, is it expected that these risks can be managed adequately by adhering to the SmPC guidance as most physicians are familiar with them.

Indeed, CNS events are more common in epileptic patients than in the normal population, and while adverse reactions such as headache and diplopia could have an impact on the quality of life of patients, the clinical impact of these risks on patients is considered minimal in relation to the severity of the indication.

In the post-marketing period up to 20 November 2020, there were 125 somnolence (1 serious), 84 dizziness, 21 blurred vision, 10 confusional state, 0 ataxia, 8 irritability (1 serious), 25 diplopia (1 serious), 137 fatigue (1 serious), 3 abnormal coordination, 67 headache (1 serious),11 dysarthria, 1 nystagmus, 4 aphasia (1 serious), and 26 memory impairment spontaneous cases reported.

- Skin reactions

Adverse events of special interest were created for the cenobamate clinical development program after the 3 cases of DRESS were identified to assess potential safety risks related to a broader category of skin reactions. Skin reactions were identified using the customised MedDRA query (CMQ) which included the preferred terms (PTs) dermatitis allergic, drug eruption, eczema, erythema, exfoliative rash, eosinophilic cellulitis, eosinophilic dermatitis, rash, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papulosquamous, rash pruritic, rash vesicular, skin exfoliation, toxic skin eruption, urticaria, angioedema, eyelid oedema, swelling face, drug hypersensitivity, facial oedema, photosensitivity reaction, and pruritus.

In the long-term open label studies (Phase 2/3 Pool), 176 patients (9.0%) (95% CI 7.8, 10.4) treated with cenobamate reported skin reactions (Data Package 3 Table SVII.1.1). The most frequency reported TEAEs in the Skin and subcutaneous tissue disorders system organ class (SOC) were pruritus (n=47, 2.4%), rash (n=47, 2.4%), erythema (n=15, 0.8%) and urticaria (n=14, 0.7%). Overall, the majority of skin reactions TEAEs that were reported with patients treated with cenobamate in the Phase 2/3 Pool were non-serious and of mild or moderate severity (Data Package 3 Table SVII.3.3). Of the 176 patients (9.0%) with reported skin reactions this included 137 (7.0%) of mild severity, 38 (2.0%) of moderate and 1 (0.1%) of severe severity. The severe skin reaction (erythema) occurred in a patient 8 days after starting treatment with cenobamate 100 mg (assessed as related to cenobamate) in Study C017 (Data Package 3 Listing SVII.3.7). Cenobamate was withdrawn and the patient recovered. A total of 7 patients (0.4%) reported serious skin reactions and of these 2 (0.1%) were of mild and 5 (0.3%) of moderate severity (Data Package 3 Table SVII.3.2).

In the double-blind pool the overall frequency of skin reactions was comparable for patients treated with cenobamate (Overall Cenobamate Group N = 442) N=17 (3.8%) (95% CI 2.3, 6.1) and those receiving placebo N=7 (3.2%) (95% CI 1.3, 6.6) (Data Package 3 Table SVII.1.2). In the Overall Cenobamate Group the most frequency reported TEAEs in the Skin and subcutaneous tissue disorders SOC were pruritus (n=5, 1.1%) and rash (n=4, 0.9%) (Data Package 3 Table SVII.3.4). Overall, the majority of skin reactions TEAEs that were reported with patients treated with cenobamate (Overall Cenobamate Group N = 442) in the Double-blind Pool were non-serious and of mild or moderate severity (Data Package 3 Table SVII.3.6). Of the 17 patients (3.8%) treated with cenobamate with reported skin reactions this included 9 (2.0%) of mild severity, 7 (1.6%) of moderate and 1 (0.2%) of severe severity. The severe skin reaction (erythema) was the same patient from Study C017 who experienced erythema 8 days after starting treatment with cenobamate 100 mg (assessed as related to cenobamate) (Data Package 3 Listing SVII.3.8). Cenobamate was withdrawn and the patient recovered. In the double-blind pool only 1 patient (0.2%) treated with cenobamate reported a serious skin reaction of drug hypersensitivity of moderate severity (n=1, 0.2%) (Data Package 3 Table SVII.3.5). No serious skin reaction TEAEs were reported in patients treated with placebo. The occurrence of reactions overall did not increase with dose; Cenobamate 100 mg (N=108): 7 (6.5%), Cenobamate 200 mg (N=223): 8 (3.6%), and Cenobamate 400 mg (N=111): 2 (1.8%).

There were no cases of Stevens Johnson Syndrome or Toxic Epidermal Necrolysis in either the Phase 2/3 Pool or the Double-blind pool.

In the post-marketing period up to 20 November 2020, there were a total of 85 (2 serious) adverse reactions reported relating to the Skin and subcutaneous tissue disorders SOC. The most frequently reported adverse reactions were 33 rash (1 serious) and 18 pruritus. There were no cases of Stevens Johnson Syndrome or Toxic Epidermal Necrolysis. There was 1 serious case of DRESS reported (Module SVII.3).

Skin reactions observed in the clinical development programme and during the post-marketing period were generally non-serious and of mild or moderate severity and are not considered an important risk of cenobamate.

Known risks that require no further characterisation for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice):

- Increase in phenytoin and phenobarbital plasma levels

  Cenobamate has been shown to increase plasma levels of phenobarbital and phenytoin.

  In a study in healthy subjects, concomitant administration of cenobamate 200 mg/day and phenytoin 300 mg/day slightly reduced cenobamate exposures (C_{max} by -27%, AUC by -28%), and increased phenytoin exposures (C_{max} by 67%, AUC by 84%). No dose adjustment of cenobamate is required but phenytoin concentrations should be monitored during titration of cenobamate, and based on individual response, the dose of phenytoin may need to be reduced.

  In a study in healthy subjects, concomitant administration of cenobamate 200 mg/day and phenobarbital 90 mg/day did not cause clinically meaningful changes in cenobamate exposure but led to increased phenobarbital exposures (C_{max} by 34% and AUC by 37%). No dose adjustment of cenobamate is required. Concentrations of phenobarbital should be monitored during cenobamate titration, and based on individual response, the dose of phenobarbital may need to be reduced.

  The drug-drug interactions are not considered important as they can be managed through standard clinical practice for prescribing phenobarbital and phenytoin and through the Ontozry SmPC guidance that describes the interactions and the recommended monitoring for healthcare professionals.

- Interaction with oral contraceptives at cenobamate doses >100 mg daily

  Many anti-epileptic drugs typically have drug-drug interactions with oral contraceptives, or with CYP450 enzymes utilised in the metabolism of oral contraceptives, requiring alternative forms of birth control. A drug-drug interaction study of cenobamate with oral contraceptives was performed. In the study, no statistically significant interaction was found. However, the dose of cenobamate was only 100 mg, rendering the finding of no significant interaction inconclusive for the treatment of female patients using contraceptives and receiving higher therapeutic doses of cenobamate.

  In a probe study using midazolam as an index substrate to assess the effect of 100 mg/day and 200 mg/day cenobamate on CYP3A4 (which also metabolises oestrogens and progesterone), significant interactions were found, where midazolam exposures (AUC) were reduced by 27% and 70%, respectively. The results of this study provide sufficient clinical evidence that cenobamate at recommended therapeutic doses of 200 mg/day up to 400 mg/day would decrease plasma levels of oral contraceptives.

  The Ontozry SmPC informs healthcare professionals that cenobamate showed a dose-dependent induction of CYP3A4, reducing exposures (AUC) of the CYP3A4 substrate, midazolam 2 mg by 72% with cenobamate 200 mg/day. Since hormonal contraceptives may also be metabolised by CYP3A4, their efficacy may be reduced by concomitant use with cenobamate. Therefore, women of

reproductive potential concomitantly using oral contraceptives are advised to use additional or alternative non-hormonal birth control.

It is expected that this risk, while important can be managed adequately based upon the SmPC guidance, and it is expected that physicians treating patients with AEDs are conscious of the risks to human reproduction. Thus, the interaction of cenobamate with oral contraceptives is not considered an important risk.

Other reasons for considering the risks not important:

- Potential for abuse and dependence

  At the request of the FDA the XCOPRI® prescribing information presents cenobamate as a controlled substance (Schedule V). Schedule V in the US includes a number of anti-epileptic drugs such as Biviact (brivaracetam) or Vimpat (lacosamide) which remain non-controlled substances in the EU.

  Following single ascending dose administration of cenobamate up to 750 mg in healthy patients, there were no reports of euphoric or elevated mood, feeling drunk, or feeling abnormal (DAPA report).

  As discussed in Module SVI.1, Arvelle considers that the potential for abuse and dependence to be low. While there were some findings suggestive of abuse potential these were observed with the higher than recommended dose (400 mg/day) in recreational sedative abusers in a dedicated human abuse potential study. However, the abuse potential of cenobamate at doses up to 400 mg/day has been shown to be less than that of therapeutic doses of alprazolam. Clinical adverse event data in that study suggest that the potential euphoric and sedative effects associated with cenobamate are less than those of a benzodiazepine (Module 2.7.2 Section 2.5.3).

  In study C024, the rate of euphoric mood AEs in the cenobamate 400 mg arm was similar to that observed with alprazolam 1.5 mg and 3.0 mg arms, but no instances of euphoric mood were observed in the cenobamate 200 mg arm. The overall incidence of euphoric mood in patients (0.3%) is comparable to that reported for the unscheduled AED, eslicarbazepine (0.1-1%, Zebinix SmPC).

  Seven (0.3%) patients experienced euphoric mood in the Phase 2/3 pool and all events occurred at doses <400mg. None of these patients had AEs associated with suicidal thoughts.

  In the post-marketing period up to 20 November 2020, there was only 1 case of euphoric mood (non-serious) reported.

  Considering all additional abuse-related AE data it is reasonable to assume that on the market, cenobamate would be subject to significantly lower rates of abuse than Schedule IV benzodiazepines such as alprazolam, and would be subject to minimal abuse in the community. Overall, cenobamate has a low potential for abuse in patients.

  The potential for abuse and dependence is not considered an important risk as Arvelle considers the risk for cenobamate to be low compared with other products that are readily abused. The risk will continue to be monitored in clinical practice using routine pharmacovigilance.

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

Important Identified Risk 1: Drug rash with eosinophilia and systemic symptoms (DRESS)

DRESS was first described in association with AEDs and it was therefore named anticonvulsant hypersensitivity syndrome (Shear and Spielberg 1988). Typical clinical picture of the DRESS includes fever, skin eruption, eosinophilia, and multiple organ involvement (lymph node enlargement, hepatitis, pneumonitis, renal dysfunction, etc.). The incidence of DRESS is estimated to vary from 1 in 1000 to 10,000 (Criado 2012). In most patients with DRESS, the symptoms disappear when the administration of an offending drug is ceased, however, a fatal outcome is reported in 10–40% of affected individuals (Gogtay 2005; Peyriere 2006). A diagnosis of DRESS is based upon a combination of clinical observations, including a history of drug exposure, cutaneous findings, systemic findings (such as fever, lymphadenopathy, visceral involvement), and laboratory findings. DRESS has a known association with established anticonvulsants (carbamazepine, lamotrigine, phenobarbital, phenytoin, oxcarbazepine, gabapentin) and DRESS syndrome usually presents 2 to 6 weeks (uncommonly 8 to 16 weeks) after the start of exposure to a drug.

The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) has developed a scoring system to aid diagnosis of suspected DRESS cases (Roujeau, 2009).

In November 2015, the FDA placed the cenobamate development program on Partial Clinical Hold and requested that the sponsor ([CCI]) further characterise the safety signal and examine the safety database to identify all suspected cases of DRESS and determine their causality. The entire safety database, [PPD], was examined. Sponsor [CCI] conducted a search of AE tables and listings for all studies using search terms derived from the European RegiSCAR Project criteria for DRESS and from literature review. Search criteria were based on a list of MedDRA preferred terms associated with the signs and symptoms of DRESS such as rash, fever, lymphadenopathy and eosinophilia. [CCI] applied a RegiSCAR scoring system to suspected DRESS cases and confirmed the diagnosis for 3 cases. In addition, Sponsor [CCI] requested external consultation from 2 experts, Dr [CCI/PPD]) and Dr [CCI/PPD] (to confirm accurate scoring and DRESS identification.

[CCI] Sponsor performed an aggregate analysis of all cases of rash/hypersensitivity identified in cenobamate studies of epilepsy patients and healthy volunteers to January 2016 ([CCI] Sponsor Complete Response 2016). The analysis included rash, angioedema, urticaria and swelling of face, skin or mucous membranes any time after initiating cenobamate administration, irrespective of any concomitant medication. This analysis included 833 patients/subjects treated with cenobamate and 301 treated with placebo. The rate of rash/hypersensitivity and DRESS by initial dose and titration rate in patients/subjects exposed to multiple doses of cenobamate or placebo are presented in Table Part II.11.

Table Part II.11 - Occurrence of rash/hypersensitivity and DRESS in patients/subjects exposed to multiple doses of cenobamate in clinical studies

	Number (%) of Patients/Subjects							
	Starting dose 50 mg with 50 mg increase every 2 weeks		Starting dose 50 mg with 50 mg increase every 1 week		Starting dose ≥100 mg with 100 mg increase every 5 to 7 days		Total	
	Cenobamate	Placebo	Cenobamate	Placebo	Cenobamate	Placebo	Cenobamate	Placebo
Patients/subjects	120	112	363	152	350	37	833	301
Rash/ hypersensitivity	1 (0.8)	3 (2.7)	18 (5.0)	4 (2.6)	19 (5.4)	3 (8.1)	38 (4.6)	10 (3.3)
Dropouts	1 (0.8)	0 (0.0)	8 (2.2)	1 (0.6)	9 (2.5)	0 (0.0)	18 (2.2)	1 (0.3)
DRESS	0	0	1	0	2	0	3	0

Abbreviations: DRESS=drug reaction with eosinophilia and systemic symptoms.
Source data: [CCI] Sponsor Complete Response, Table 7

The results of the aggregate analysis suggest that cenobamate titration rate and starting dose may impact on the rate of rash/hypersensitivity:

- When cenobamate the dose was increased weekly or faster, steady state blood concentrations had not been reached before the next dose increment. Cenobamate has a half-life of 55 hours and takes 10 to 12 days to reach steady state. Under these circumstances the rate of rash/hypersensitivity reaction was approximately 5%. When cenobamate dosing started at 50 mg and was increased in 50 mg increments every 2 weeks, steady state was reached before the next dose increment and very few hypersensitivity reactions (1 case, 0.8%) were observed.
- At a starting dose of ≥100 mg the rate of rash/hypersensitivity was 5.4% (19 of 350 patients/ subjects). When the starting dose was 50 mg the rate of rash/hypersensitivity was 3.9% (19 of 483 patients/subjects).

The 3 DRESS cases occurred in cenobamate studies that had rapid titration to target dose. Two cases occurred when the initial cenobamate dose was 100 mg or 200 mg followed by rapid titration. The third case, in a healthy volunteer, occurred in a study where the initial cenobamate dose was 50 mg/day for 1 week and was increased by 50 mg weekly increments. Although the number of patients/subjects with DRESS is small, there was a potential for a similar trend relating the impact of the initial cenobamate dose and subsequent titration rate on the frequency of DRESS. With a starting dose of 50 mg the estimated rate of DRESS was 0.21% (1 of 483 patients/subjects) and when the starting dose was ≥100 mg the estimated rate of DRESS was 0.57% (2 of 350 patients/subjects).

Experience of DRESS and hypersensitivity reactions with licenced medications

It has been demonstrated that the slow up-titration of many medicines (e.g. antidepressants, painkillers etc.) can reduce the occurrence of DRESS and hypersensitivity side effects. This approach has been successfully utilised with lamotrigine to reduce the risk of serious rash (Wong 1999) and nevirapine (Barreiro 2000) to reduce the rates of drug reactions and rash.

Analysis of clinical trial data showed an association between high starting dose and rash and the lamotrigine dosing recommendations (for both starting dose and titration rate) were revised. Wong (1999) reported data from a retrospective survey of 5 tertiary epilepsy referral centres in the UK evaluating the occurrence of rash and serious rash before and after lamotrigine dosing revision; the incidence to serious rash prior to dose regimen change was 12 of 805 treated patients (1.5%) and after revisions was 0 of 245 treated patients.

Barreiro et al. (2000) in their article 'Prevention of nevirapine-associated exanthema using slow dose escalation and/or corticosteroids' describe a similar rash mitigation strategy: they stated that 'the incidence of rash complicating the first few weeks of treatment with nevirapine can be diminished by adding corticosteroids for 2 weeks to the standard recommendation, or by using a slowly escalating the dose. This second approach is proven to be pharmacokinetically safe.'

The 3 cases of DRESS occurred in cenobamate studies with fast titration to the target dose. Two cases occurred when the initial cenobamate dose was 100 or 200 mg/day followed by rapid titration. The third case occurred in a study where the initial cenobamate dose was 50 mg/day for 1 week followed by dose increase at 50 mg increments. As a result, a lower cenobamate starting dose and slower titration rate was implemented in subsequent studies to mitigate the potential for morbidity and mortality associated with DRESS.

Since the decision to use a slower cenobamate titration rate and lower starting dose, no cases of DRESS have been identified in the 1340 patients exposed to at least 1 cenobamate dose in Study C021, including 1138 patients exposed for at least 6 months (median exposure for Study C021, 98.6 months).

In the post-marketing period up to 20 November 2020, 1 serious case of DRESS was reported. In this case ([PPD]) a [PPD] patient was treated with 50 mg cenobamate and experienced DRESS. The titration schedule and previous dosing were not known. The action taken with the drug and the outcome were unknown. Medical history and concomitant medications were not known. The Sponsor considered the adverse reaction possibly related to treatment. Additional follow-up information has been requested.

Risk-benefit impact: DRESS has been classified as an important identified risk due to its seriousness and potential severity. Although DRESS events were rare in the clinical program of cenobamate, there is a possibility that they occur as life-threatening events or lead to a serious outcome and discontinuation of treatment. The titration schedule of cenobamate was specifically designed for prevention of DRESS, and it was developed in close collaboration with a stringent health authority (FDA). Subsequent to the implementation of the current titration schedule, no cases of DRESS have been seen in Study C021.

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the risk of DRESS which can be managed in clinical practice by using the recommended initial dose and titration schedule and through patient monitoring in clinical practice.

Important Potential Risk 1: Hypersensitivity

Hypersensitivity was identified using the customised MedDRA query (CMQ) that included the following preferred terms (PTs): hypersensitivity, drug hypersensitivity and eyelid oedema.

In the long-term open label studies (Phase 2/3 Pool), 13 patients (0.7%) (95% CI 0.4, 1.1) treated with cenobamate reported hypersensitivity (Table 15). The majority of the hypersensitivity TEAEs were from the Immune system disorders SOC (n=11, 0.6%) including drug hypersensitivity (n=5, 0.3%) and hypersensitivity (n=6, 0.3%) with a small number of Eye disorders TEAEs (eyelid oedema n=2, 0.1%) (Table 16). Overall, the majority of hypersensitivity TEAEs that were reported with patients treated with cenobamate in the Phase 2/3 Pool were non-serious and of mild or moderate severity. Of the 13 patients (0.7%) treated with cenobamate with hypersensitivity this included 7 (0.4%) of mild severity and 6 (0.3%) of moderate severity (Table 16). No severe hypersensitivity TEAEs were reported.

Only a patient (0.1%) treated with cenobamate reported a serious TEAE of drug hypersensitivity of moderate severity (n=1, 0.1%) (Table 16). In this case, considered related to cenobamate per the investigator's assessment, the patient [PPD] experienced drug hypersensitivity after 1 day of cenobamate treatment (Data Package 3 Listing SVII.3.9all23). Cenobamate treatment was withdrawn and the patient recovered.

Hypersensitivity was assessed in the double-blinded pooled dataset where the overall frequency of skin reactions was comparable for patients treated with cenobamate (Overall Cenobamate Group N = 442) N=4 (0.9%) (95% CI 0.2, 2.3) and those receiving placebo N=1 (0.5%) (95% CI 0.0, 2.6) (Table 17). The majority of the skin reactions TEAEs in the Overall Cenobamate Group were from the Immune system disorders SOC (n=3, 0.7%) including drug hypersensitivity (n=3, 0.5%) and hypersensitivity (n=1, 0.2%), and there was 1 eye disorders TEAE (eyelid oedema n=1, 0.2%).

Overall, the majority of hypersensitivity TEAEs that were reported with patients treated with cenobamate (Overall Cenobamate Group N = 442) in the Double-blind Pool were non-serious and of mild or moderate severity (Table 18). Of the 4 patients (0.9%) treated with cenobamate with hypersensitivity this included 1 (0.2%) of mild severity and 3 (0.7%) of moderate severity (Table 18). No severe hypersensitivity TEAEs were reported.

Only a patient (0.2%) treated with cenobamate reported a serious TEAE of drug hypersensitivity of moderate severity (n=1, 0.2%) (Table 18). This was the same case from Study C013 (reported in the Phase 2/3 pool), considered related to cenobamate per the investigator's assessment, in which the patient experienced drug hypersensitivity after 1 day of cenobamate treatment (Data Package 3 Listing SVII.3.9). Cenobamate treatment was withdrawn and the patient recovered.

No serious skin reaction TEAEs were reported in patients treated with placebo. The patient treated with placebo experienced a non-serious hypersensitivity TEAE that was of mild severity (n=1, 0.5%) (Table 18).

There were no other severe adverse events indicative of systemic hypersensitivity other than DRESS that is classified separately as an important identified risk.

The database was searched for additional terms that might be related to hypersensitivity. No severe cases have been identified. Of note, there was one case of swelling face reported in the Double-blind Pool dataset occurring at 100 mg cenobamate. However, this case Verbatim Term entered by the investigator was "Left Side Facial Swelling" which is indicative of a local, and not systemic process. This case was rated moderate in severity, resolved with no cenobamate dose change after 3 days, and was considered not related to cenobamate per the investigator's assessment. Given the localised nature of this single AE, it was not included in the group of terms for hypersensitivity as it was not likely to represent systemic hypersensitivity reactions.

In the post-marketing period up to 20 November 2020, there were 5 hypersensitivity spontaneous cases reported, none of which was serious. No cases of anaphylaxis or anaphylactoid reactions were reported.

Risk-benefit impact:

Hypersensitivity has been observed with cenobamate treatment in the clinical development programme.

Hypersensitivity (including the following terms hypersensitivity, drug hypersensitivity, and eyelid oedema) is an uncommon (≥ 1/1,000 to < 1/100) adverse reaction in the Ontozry SmPC that could be serious and potentially life-threatening if not managed appropriately.

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of hypersensitivity that can be managed in clinical practice by adhering to the SmPC guidance.

Important Potential Risk 2: Suicidality (class effect)

Suicidality-related events have been reported more often in people with epilepsy, than in the general population (Mula 2011; Bell 2009). In patients with epilepsy, the prevalence of suicidal thoughts is 2–3 times higher than in those without epilepsy (Tellez-Zenteno 2007; Christensen 2007). Furthermore, suicide appears to be associated with chronic, drug resistant epilepsy (Mbizvo 2019).

An increase in suicidal ideation and behaviour has been recognised across epilepsy patients and epilepsy patients taking anti-epileptic drugs (AEDs). In the long-term open label studies (Phase 2/3 Pool), 46 unique patients (2.4%) (95% CI, 1.7, 3.1) reported events related to suicidal ideation or behaviour with the majority (N=35, 1.8%) experiencing suicidal ideation **(**Table Part II.18). Suicidal behaviour and ideation was assessed in the double-blinded pooled dataset where the overall frequency of suicidal behaviour and ideation was comparable for patients treated with cenobamate N=5 (1.1%) (95% CI, 0.4, 2.6) and those receiving placebo N=1 (0.5%) (95% CI 0.0, 2.6) (Table 21). The majority of patients experienced suicidal ideation (N=4, 0.9% patients treated with cenobamate and N=1, 0.5% patients treated with placebo) (Table Part II.20).

While there were events of suicidal ideation and behaviour including 2 completed suicides in the Phase 2/3 Pool, frequencies in the double-blind pooled dataset were comparable to placebo, and in the long-term open-label studies, less than a third of adverse events (16 of 55 AEs) occurred within 6 months of starting cenobamate treatment and as such the temporal relationship does not support causality.

In the post-marketing period up to 20 November 2020, there was 1 suicide attempt (serious), 8 suicidal ideation (all serious), and 1 intentional self-injury. While 8 of these 10 cases show a temporal relationship and 4 cases show a positive dechallenge (2 cases have limited information), 6 of the 10 reported cases detail relevant medical history (suicidal thoughts; bipolar disorder and suicidal thoughts; 2 depression; anxiety; and ‘problems mentally’), Other possible confounding factors are co-suspect drugs reported in 5 cases (olanzapine and lithium; eslicarbazepine acetate and clobazam; topiramate, lamotrigine, zonisamide, phenytoin, and clonazepam; 2 levetiracetam).

Risk-benefit impact:

Based upon the clinical data available, no increased risk of suicidality associated with cenobamate can be determined. Nevertheless, as suicidal behaviour and ideation is a known class effect of AEDs, suicidality is classified as an important potential risk.

It is reasonable to assume that prescribers will be familiar with the management of this complication of treatment with AEDs. The risk of suicidality with cenobamate has been adequately characterised in the clinical development programme and therefore routine pharmacovigilance activities are proposed. The risk will be managed in clinical practice through routine risk minimisation measures in line with the risk management plans available for other medications. The Ontozry SmPC stipulates the class wording established for other AEDs in the EU. Healthcare professionals are informed of the risk and advised that patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Furthermore, patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of suicidality that is recognised to occur with AEDs and can be managed in clinical practice through patient monitoring.

Important potential risk 3: QT shortening

QT shortening seen in the cenobamate clinical development programme is of unclear clinical significance and did not result in medical consequences.

In a Phase 1 Thorough QT Study (C020) in healthy volunteers evaluating the effects of 200 mg/day (therapeutic) and 500 mg/day (supratherapeutic) doses of cenobamate, the placebo-corrected change in QTcF from baseline was predicted as -9.85 msec (90% CI -11.61, -8.10) at the observed geometric mean peak plasma level of cenobamate on Day 35 (23.06 µg/mL), and as -17.14 msec (90% CI -19.48, -14.79) at the observed geometric mean peak plasma level on Day 63 (63.96 µg/mL) (CSR C020, Appendix 16.2.10, Table 2). There was a decrease in QTcF with increasing doses of cenobamate, with the largest effect at 0.5

hour, -10.8 msec (90% CI: -13.4 to -8.2) on Day 35 (200 mg) and -18.4 msec (90% CI: -21.5 to - 15.2) on Day 63 (500 mg). However, no subjects had QTcF values <340 ms (Data Package 1 Question 128, Table 2), and no treatment-emergent or significant atrial or ventricular arrhythmias were recorded on ECG or reported as adverse events during the double-blind treatment part of the study [C020 CSR Appendix 16.2.8.8 and Table 14.3.1.1].

In the double-blind pooled dataset, relatively small decreases in mean QTcF were noted for cenobamate (-2.3, -3.0 and –8.2 ms for 100, 200 and 400 mg respectively) and for placebo (-0.7 ms) at end of titration and for cenobamate (–2.4, -1.9, -3.7 for 100, 200 and 400 mg respectively) and placebo (-1.3 ms) at end of double-blind treatment (MAA 2.7.4 Table 122). ECG interpretation statements from ECGs obtained during the double-blind treatment phase revealed no treatment-emergent clinically significant atrial or ventricular arrhythmias in any treatment group [ISS Appendix C, Table 9.3.1]

In the post-marketing period up to 20 November 2020, there was 1 non-serious case of supraventricular extrasystoles reported. There were no cases of QT shortening or other cardiac arrhythmias reported.

In vitro tests on the cardiovascular system with sodium channels, rabbit Purkinje fibers, and human ether-à-go-go-related gene (hERG) showed some potential for effects including 1) shortened duration of the action potential and 2) lowering or depression of the plateau phase of action potential at ≥100μM (Module SII). However, cenobamate had no effects on cardiac (electrocardiogram [ECG]) or circulatory function as measured by telemetry in monkeys at single PO doses of 4, 12, and 36 mg/kg. Cenobamate was classified as low-risk hERG channel blocker with an IC50 of 1,869 μM. In addition, no evidence of cardiotoxicity was found in in vivo toxicity studies, including histopathologic evaluations of rats and monkeys.

Risk-benefit impact:

Data from healthy subjects in the QT Study C020 shows that cenobamate is associated with dose-dependent shortening of the QT interval. In the double-blind pooled dataset, the magnitude of the effect was much smaller. In the current literature there is no evidence of a QT shortening non-antiarrhythmic drug increasing the risk of repolarization related arrhythmias in humans (Module SVII.3). The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of QT shortening that is of unclear clinical significance in adult populations and can be managed in clinical practice through healthcare professional awareness and clinical judgement for use of cenobamate in patients with Familial Short QT Syndrome.

Important potential risk 4: Reproductive/embryofoetal toxicity

To date there are no adequate data on the developmental risk associated with the use of Ontozry in pregnant women.

Female patients/subjects who were pregnant or lactating were excluded from enrolling in the cenobamate clinical studies. However, in total 19 cenobamate-treated patients/subjects had 20 pregnancies reported across the clinical development programme through June 2020. The outcome of the pregnancies included 7 live births (normal), 2 ectopic pregnancies, 3 spontaneous abortions, 4 elective terminations and in 3 cases the outcome was unknown. A summary of those patients/subjects reporting pregnancy is presented in Table Part II.28.

In the postmarketing period up to 20 November 2020, 5 spontaneous cases of maternal exposure during pregnancy were reported in the USA, one of which also reported spontaneous abortion (Module SVII.3).

While data in humans are limited, non-clinical studies in the rat have shown embryofoetal mortality, neurobehavioural effects and impairment in offspring (Module SII).

The Ontozry SmPC recommends that women of childbearing potential use effective contraception during treatment with cenobamate in the Ontozry SmPC. Women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control since hormonal contraceptives are metabolised by CYP3A4 and their efficacy may be reduced by concomitant use with cenobamate.

Cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment with cenobamate. The Ontozry SmPC also contains the class wording for AEDs which states that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the underlying condition is responsible has not been elucidated. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Risk-benefit impact:

The currently available dataset is not sufficient to assess the potential impact of cenobamate on human reproduction. This represents a gap in knowledge and reproductive/embryofoetal toxicity will be further characterised using additional pharmacovigilance via EURAP - An International Registry of Antiepileptic Drugs and Pregnancy (Part III.2).

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the risk of reproductive/embryofoetal toxicity that can be managed in clinical practice through use of effective contraception and awareness of the risks. As the product is available only by prescription, it can be reasonably assumed that physicians will weigh the potential risks and expected benefits prior to prescribing cenobamate.

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

After an independent re-assessment of data from EudraVigilance related to the PSUSA procedure EMEA/H/C/PSUSA/00010921/202303), the PRAC considered that a causal association between the use of cenobamate and the onset of suicidal ideation represents a reasonable possibility. Therefore, in order to better document the risk of suicidality, the PRAC requested the MAH to reclassify the Important potential risk of “Suicidality (class effect)” as an Important identified risk re-named as “Suicidality”, and to update sections 4.4 and 4.8 of the SmPC.

Accordingly, the risk *Suicidality (class effect)* previously classified as **important potential risk** has been re-named as *Suicidality* and reclassified as an **important identified risk.**

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

Important identified risk 1: Drug rash with eosinophilia and systemic symptoms (DRESS)

Potential mechanisms:

DRESS is a drug-induced, multiorgan systemic hypersensitivity reaction common to many antiepileptic drugs. The exact mechanism is unknown.

Evidence source and strength of evidence:

Three cases of DRESS were seen in the clinical development of cenobamate in clinical studies with high starting doses and rapid titration. In large safety study designed to mitigate the risk of DRESS utilizing a lower starting dose and slower titration scheme there were no additional cases of DRESS seen in 1340 patients.

Characterisation of the risk:

There were 3 confirmed cases of DRESS in the cenobamate clinical programme, i.e. 3 of 2479 subjects treated with cenobamate in Phase I to Phase III, or 0.1%. All three cases occurred with a high starting dose or high titration rate. The observation of DRESS in the cenobamate programme led to the design of the long-term safety study C021 (1340 patients) and lower starting dose (12.5 mg) and slower titration rate (2-weekly dose increase) in order to demonstrate no cases of DRESS, with an upper limit of the 95% CI of the DRESS rate of <0.003. In study C021, DRESS was not reported in 1340 patients with a total of 2191.7 patient-years exposure (MAA 2.7.4 Table 18), underlining the effectiveness of the revised dosing regimen to abolish the occurrence of DRESS in patients treated with cenobamate. No cases of DRESS have been seen in clinical studies with titration rates of 2-weekly dose increments.

The incidence of DRESS in the all Phase 2/3 pool and double-blind pool is provided in Table Part II.12 and Table Part II.13 , respectively.

Table Part II.12 - Incidence of Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) - All Phase 2/3 Pool

Important Identified Risk	Statistics	Overall Cenobamate (N = 1945)
DRESS	n (%)	1 (0.1%)
	95% CI	(0.0, 0.3)

Abbreviations: CI = confidence interval; Drug reaction with Eosinophilia and Systemic Symptoms (DRESS).
n under each risk refers to the number of subjects to the concerned risk. Subjects with multiple events under the same risk is counted only once under the corresponding risk.
Percentages are based on the overall N = 1945 used as denominator.
95% CI of % based on exact binomial distribution.
Data cut as of June 01, 2020. Source: Data Package 3 Table SVII.1.1

Table Part II.13 - Incidence and comparisons of Drug reaction with Eosinophilia and Systemic Symptoms (DRESS) – Double-blind pool

Important Identified risk	Statistics	Overall Cenobamate (N = 442)	Cenobamate 100 mg (N = 108)	Cenobamate 200 mg (N = 223)	Cenobamate 400 mg (N = 111)	Placebo (N = 216)
DRESS	n (%)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
	95% CI	(0.0, 1.3)	(0.0, 3.4)	(0.0, 2.5)	(0.0, 3.3)	(0.0, 1.7)
	Relative risk (RR) vs Placebo	NE	NE	NE	NE	
	95% CI of RR	[NE, NE]	[NE, NE]	[NE, NE]	[NE, NE]	

Abbreviations: CI = confidence interval; DRESS = drug reaction with eosinophilia and systemic symptoms, RR = relative risk.
n under each risk refers to the number of subjects to the concerned risk. Subjects with multiple events under the same risk is counted only once under the corresponding risk.
Percentages are based on the overall N = 1945 used as denominator.
95% CI of % based on exact binomial distribution.
Relative risk < 1 indicates a lower risk vs placebo, and > 1 indicates a higher risk vs placebo.
Data cut as of July 01, 2019 Source: Data Package 3 Table SVII.1.2

One case of confirmed DRESS was reported in the double-blind Phase 2/3 pool. This event occurred in Study C017:

- Subject [PPD]: The subject's initial cenobamate dose was 100 mg, increased to 200 mg over 1 week.

In addition, there were 2 confirmed cases in the Phase 1 pool.

- Subject [PPD] in Study C018: The subject's initial cenobamate dose was 200 mg followed by 100 mg increments every 5 days. On Day 14 of the study, the subject reported an SAE of DRESS that required hospitalisation. The subject discontinued treatment and the DRESS resolved.
- Subject [PPD]in Study C020: The subject's initial cenobamate dose was 50 mg/day for 1 week followed by 50 mg increments every 7 days. The [PPD] subject experienced the SAE of DRESS syndrome that began on Day 32 of dosing with cenobamate, and subsequently died from the SAE of eosinophilic myocarditis on Day 87. The SAE was considered as related to cenobamate.

The risk of DRESS and associated signs/symptoms can be mitigated/reduced with use of a lower initial dose (12.5 mg/day) and an every 2-week titration schedule of cenobamate. Since the decision to use a slower cenobamate titration rate and lower starting dose, no cases of DRESS have been identified in the 1340 patients exposed to at least 1 cenobamate dose in Study C021, including 1134 patients exposed for at least 6 months (median exposure for Study C021, 98.6 weeks).

In the post-marketing period up to 20 November 2020, 1 serious case of DRESS was reported. In this case ([PPD]) a [PPD]patient was treated with 50 mg cenobamate and experienced DRESS. The titration schedule and previous dosing were not known. The action taken with the drug and the outcome were unknown. Medical history and concomitant medications were not known. The Sponsor considered the adverse reaction possibly related to treatment. Additional follow-up information has been requested.

Risk factors and risk groups:

Rapid titration and initiating treatment at a higher starting dose.

Preventability:

The risk of DRESS can be minimised by adhering to the guidance in the SmPC to initiate cenobamate at a dose of 12.5 mg and an every 2-week titration schedule of cenobamate. Utilising this titration schedule in Study C021 there were no cases of DRESS seen in 1340 patients enrolled.

Furthermore, healthcare professionals are advised to monitor patients for signs / symptoms including The results of the aggregate analysis suggest that cenobamate faster titration rate and higher starting dose may impact on the rate of DRESS.

Impact on the risk-benefit balance of the product:

There is a high unmet medical need for new AEDs that can target seizure freedom in patients with focal onset seizures, not adequately controlled with two or more AEDs.

Many patients continue to experience a diminished quality of life while receiving existing therapies because the currently available drugs fail to adequately control their seizures. Cenobamate is efficacious at reducing the frequency of focal-onset seizures in patients with treatment resistant epilepsy and increasing the rate of seizure freedom.

DRESS is recognized as a serious drug reaction, and while most cases can be successfully medically managed there remains a risk of fatality. Nonetheless, DRESS is a known risk for many antiepileptic drugs and has been accepted into medical management of patients with treatment resistant epilepsy.

With the slower titration scheme, the risk of DRESS has been successfully mitigated. The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the risk of DRESS which can be managed in clinical

practice by using the recommended initial dose and titration schedule and through patient monitoring in clinical practice.

Public health impact:

The public health impact of DRESS with cenobamate is considered to be low given the rarity of DRESS with cenobamate and that the risk of DRESS can be minimised with the recommended initial dose and titration schedule.

Important identified risk 2: Suicidality

Potential mechanisms:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications but the mechanism is not known. What seems to be established is that mood disorders represent a frequent comorbidity in epilepsy and suicide is a serious complication more frequently encountered in epilepsy rather than in the general population (Mula 2011; Bell 2009). Moreover, a subgroup of patients appears to be at risk of developing treatment-emergent psychiatric adverse effects of AEDs independently of the specific mechanism of action of the drug. The prior history of suicide attempt, especially preceding the onset of the epilepsy, may represent a key element explaining why what is observed is independent of the specific mechanism of the drug (Mula 2011).

Evidence source and strength of evidence:

In the pooled double-blind studies, rates of suicidal ideation and behaviours are similar for patients treated with cenobamate and placebo, and in the long-term open-label studies, for many instances of suicidal ideation or behaviour there is not enough evidence of causality based on the timing of when the patient was treated with cenobamate and when the suicidal ideation or behaviour occurred.

While there is not enough evidence from the clinical studies that cenobamate causes an increased risk of suicidal ideation and behaviour as patients with epilepsy have an increased risk, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, but the available data do not exclude the possibility of an increased risk for cenobamate.

Characterisation of the risk:

In the long-term open label studies (Phase 2/3 Pool), 46 unique patients (2.4%) (95% CI, 1.7, 3.1) reported events related to suicidal ideation or behaviour (Table Part II.18). The majority of these patients (N=35, 1.8%) experienced suicidal ideation. A total of 16 patients (0.8%) with reported serious events related to suicidal ideation or behaviour (Table Part II.19). Of the 46 patients (2.4%) with reported events related to suicidal ideation or behaviour this included 20 (1.0%) of mild severity, 12 (0.6%) of moderate and 14 (0.7%) of severe severity (Table Part II.19). For the 16 patients (0.8%) with reported serious events related to suicidal ideation or behaviour (0.0%) this included 6 (0.3%) of moderate and 10 (0.5%) of severe severity (Table Part II.19).

Overall, 55 events of suicidal nature were reported, including 2 completed suicide events (assessed as not related to the study drug), 7 suicide attempts (5 assessed as not related and 2 as related to the study drug), 1 suicidal behaviour (assessed as not related), 42 events of suicide ideation (24 assessed as not related and 18 as related to the study drug), 1 intentional self-injury (assessed as not-related), and 2 intentional overdose (1 assessed as not related and 1 as related to study drug) (Listing lsvii0407).

For the two cases of completed suicide, the first patient (study C013 OLE) completed suicide after 132 days of cenobamate treatment and the second patient (study C017 OLE) completed suicide after 3.8 years of treatment (Data Package 3 Listing SVII.4.7). Causality is not well-supported in the second case due to the absence of temporal relationship to treatment initiation. In the first case, the 4-month latency allows for causality.

Out of the reported 55 events, 37 events occurred after more than 6 months (168 days) of cenobamate exposure, and 28 events occurred after more than 300 days of cenobamate exposure. A total of 16 events occurred less than 6 months following initiation of cenobamate treatment.

Table Part II.18 - Incidence of Suicidal behaviour and ideation - All Phase 2/3 Pool

Important identified risk	Statistics	Overall Cenobamate (N = 1945) n (%) (95% CI)
Suicidal behaviour and ideation	n (%) (95% CI)	46 (2.4%) (1.7, 3.1)

MedDRA System Organ Class (SOC) Preferred Term (PT)	Overall Cenobamate (N = 1945) n (%)
Subjects with any Suicidal behaviour and ideation TEAE	46 (2.4%)
Injury, poisoning and procedural complications	2 (0.1%)
Intentional overdose	2 (0.1%)
Psychiatric disorders	46 (2.4%)
Completed suicide	2 (0.1%)
Intentional self-injury	1 (0.1%)
Suicidal behaviour	1 (0.1%)
Suicidal ideation	35 (1.8%)
Suicide attempt	7 (0.4%)

Abbreviations: CI = confidence interval; MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Percentages are based on the overall N = 1945 used as denominator.
95% CI of % based on exact binomial distribution.
A subject experiencing multiple TEAEs of the same PT/SOC/category will be counted only once within that corresponding PT/SOC/category.
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of June 01, 2020. Source: Data Package 3 Table SVII.1.1 and Data Package 3 Table SVII.4.1

Table Part II.19 - Incidence of TEAEs of Suicidal behaviour and ideation (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity - All Phase 2/3 Pool

MedDRA System Organ Class (SOC) Preferred Term (PT)	Overall Cenobamate (N = 1945) All TEAEs n (%)	Overall Cenobamate (N = 1945) Serious TEAEs n (%)	Overall Cenobamate (N = 1945) Non-serious TEAEs n (%)
Subjects with any Suicidal behaviour and ideation TEAE	46 (2.4%)	16 (0.8%)	30 (1.5%)
Mild	20 (1.0%)	0 (0.0%)	20 (1.0%)
Moderate	12 (0.6%)	6 (0.3%)	6 (0.3%)
Severe	14 (0.7%)	10 (0.5%)	4 (0.2%)
Injury, poisoning and procedural complications	2 (0.1%)	2 (0.1%)	-
Mild	0 (0.0%)	0 (0.0%)	-
Moderate	2 (0.1%)	2 (0.1%)	-
Severe	0 (0.0%)	0 (0.0%)	-
Intentional overdose	2 (0.1%)	2 (0.1%)	-
Mild	0 (0.0%)	0 (0.0%)	-
Moderate	2 (0.1%)	2 (0.1%)	-
Severe	0 (0.0%)	0 (0.0%)	-
Psychiatric disorders	46 (2.4%)	16 (0.8%)	30 (1.5%)
Mild	20 (1.0%)	0 (0.0%)	20 (1.0%)
Moderate	12 (0.6%)	6 (0.3%)	6 (0.3%)
Severe	14 (0.7%)	10 (0.5%)	4 (0.2%)
Completed suicide	2 (0.1%)	2 (0.1%)	-

Mild	0 (0.0%)	0 (0.0%)	-
Moderate	0 (0.0%)	0 (0.0%)	-
Severe	2 (0.1%)	2 (0.1%)	-
Intentional self-injury	1 (0.1%)	-	1 (0.1%)
Mild	0 (0.0%)	-	0 (0.0%)
Moderate	1 (0.1%)	-	1 (0.1%)
Severe	0 (0.0%)	-	0 (0.0%)
Suicidal behaviour	1 (0.1%)	1 (0.1%)	-
Mild	0 (0.0%)	0 (0.0%)	-
Moderate	1 (0.1%)	1 (0.1%)	-
Severe	0 (0.0%)	0 (0.0%)	-
Suicidal ideation	35 (1.8%)	7 (0.4%)	28 (1.4%)
Mild	19 (1.0%)	0 (0.0%)	19 (1.0%)
Moderate	9 (0.5%)	4 (0.2%)	5 (0.3%)
Severe	7 (0.4%)	3 (0.2%)	4 (0.2%)
Suicide attempt	7 (0.4%)	6 (0.3%)	1 (0.1%)
Mild	1 (0.1%)	0 (0.0%)	1 (0.1%)
Moderate	1 (0.1%)	1 (0.1%)	0 (0.0%)
Severe	5 (0.3%)	5 (0.3%)	0 (0.0%)

Abbreviations: MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
A subject experiencing multiple TEAEs of the same PT/SOC/category will be counted only once within that corresponding PT/SOC/category.
Subjects who experienced multiple events within a SOC or PT are counted once at the highest severity for that SOC/PT.
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of June 01, 2020. Source: Data Package 3 Table SVII.4.3

Suicidal behaviour and ideation was assessed in the double-blinded pooled dataset where the overall frequency of suicidal behaviour and ideation was comparable for patients treated with cenobamate N=5 (1.1%) (95% CI, 0.4, 2.6) and those receiving placebo N=1 (0.5%) (95% CI 0.0, 2.6) (Table Part II.20). The majority of patients experienced suicidal ideation (N=4, 0.9% patients treated with cenobamate and N=1, 0.5% patients treated with placebo) (Table Part II.20). A total of 3 patients treated with cenobamate (0.7%) had reported serious events related to suicidal ideation or behaviour, all from the cenobamate 100 mg group (Table Part II.21). The TEAE in the placebo treated patient was not considered serious (Table Part II.21). Of the 5 patients treated with cenobamate (1.1%) with reported events related to suicidal ideation or behaviour this included 1 (0.2%) of mild severity, 2 (0.5%) of moderate and 2 (0.5%) of severe severity (Table Part II.21). The patient treated with placebo (N=1, 0.5%) who experienced an event related to suicidal behaviour and ideation was assessed to be of mild severity. For the 3 patients treated with cenobamate (0.7%) with reported serious events related to suicidal ideation or behaviour (0.0%) this included 1 (0.2%) of moderate and 2 (0.5%) of severe severity (Table Part II.21) . Overall, 6 events of suicidal nature were reported, including 1 suicide attempt (5 assessed as related to cenobamate), and 5 events of suicide ideation (4 assessed as related to cenobamate and 1 as not related to placebo) (Data Package 3 Listing 4.8). Out of the reported 6 events (5 in 5 patients treated with cenobamate and 1 in a placebo-treated patient), all occurred less than 6 months following initiation of treatment (Data Package 3 Listing 4.8).

Table Part II.20 - Incidence and comparisons of Suicidal behaviour and ideation – Double Blind Pool

Important identified risk	Statistics	Overall Cenobamate (N = 442)	Cenobamate 100 mg (N = 108)	Cenobamate 200 mg (N = 223)	Cenobamate 400 mg (N = 111)	Placebo (N = 216)
Suicidal behaviour and ideation	n (%)	5 (1.1%)	3 (2.8%)	2 (0.9%)	0 (0.0%)	1 (0.5%)
	95% CI	(0.4, 2.6)	(0.6, 7.9)	(0.1, 3.2)	(0.0, 3.3)	(0.0, 2.6)

	Relative risk (RR) vs Placebo	2.443	6.000	1.937	NE	
	95% CI of RR	[0.287, 20.786]	[0.632, 57.004]	[0.177, 21.209]	[NE, NE]	

MedDRA System Organ Class (SOC) Preferred Term (PT)	Overall Cenobamate (N = 442) n (%)	Cenobamate 100 mg (N = 108) n (%)	Cenobamate 200 mg (N = 223) n (%)	Cenobamate 400 mg (N = 111) n (%)	Placebo (N = 216) n (%)
Subjects with any Suicidal behaviour and ideation TEAE	5 (1.1%)	3 (2.8%)	2 (0.9%)	0 (0.0%)	1 (0.5%)
Psychiatric disorders	5 (1.1%)	3 (2.8%)	2 (0.9%)	0 (0.0%)	1 (0.5%)
Suicidal ideation	4 (0.9%)	2 (1.9%)	2 (0.9%)	0 (0.0%)	1 (0.5%)
Suicide attempt	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: CI = confidence interval; MedDRA = medical dictionary for regulatory affairs; PT = preferred term; RR = relative risk; SOC = system organ class; TEAE = treatment-emergent adverse event.
95% CI of % based on exact binomial distribution.
Relative risk < 1 indicates a lower risk vs placebo, and > 1 indicates a higher risk vs placebo.
A subject experiencing multiple TEAEs of the same PT/SOC/category will be counted only once within that corresponding PT/SOC/category.
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of July 01, 2019 Source: Data Package 3 Table SVII.1.2 and Data Package 3 Table SVII.4.4

Table Part II.21 - Incidence of TEAEs of Suicidal behaviour and ideation (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity - Pooled Double Blind

	Overall Cenobamate (N = 442)			Cenobamate 100 mg (N = 108)			Cenobamate 200 mg (N = 223)			Cenobamate 400 mg (N = 111)			Placebo (N = 216)		
MedDRA System Organ Class (SOC) Preferred Term (PT)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)
Subjects with any Suicidal behaviour and ideation TEAE	5 (1.1%)	3 (0.7%)	2 (0.5%)	3 (2.8%)	3 (2.8%)	-	2 (0.9%)	-	2 (0.9%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Moderate	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.9%)	1 (0.9%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	2 (0.5%)	2 (0.5%)	0 (0.0%)	2 (1.9%)	2 (1.9%)	-	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Psychiatric disorders	5 (1.1%)	3 (0.7%)	2 (0.5%)	3 (2.8%)	3 (2.8%)	-	2 (0.9%)	-	2 (0.9%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Moderate	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.9%)	1 (0.9%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	2 (0.5%)	2 (0.5%)	0 (0.0%)	2 (1.9%)	2 (1.9%)	-	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Suicidal ideation	4 (0.9%)	2 (0.5%)	2 (0.5%)	2 (1.9%)	2 (1.9%)	-	2 (0.9%)	-	2 (0.9%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Moderate	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.9%)	1 (0.9%)	-	1 (0.4%)	-	1 (0.4%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	1 (0.2%)	1 (0.2%)	0 (0.0%)	1 (0.9%)	1 (0.9%)	-	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Suicide attempt	1 (0.2%)	1 (0.2%)	-	1 (0.9%)	1 (0.9%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-

Table Part II.21 - Incidence of TEAEs of Suicidal behaviour and ideation (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity - Pooled Double Blind

	Overall Cenobamate (N = 442)			Cenobamate 100 mg (N = 108)			Cenobamate 200 mg (N = 223)			Cenobamate 400 mg (N = 111)			Placebo (N = 216)		
MedDRA System Organ Class (SOC) Preferred Term (PT)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)
Mild	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Moderate	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Severe	1 (0.2%)	1 (0.2%)	-	1 (0.9%)	1 (0.9%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-

Abbreviations: MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
A subject experiencing multiple TEAEs of the same PT/SOC/category will be counted only once within that corresponding PT/SOC/category.
Subjects who experienced multiple events within a SOC or PT are counted once at the highest severity for that SOC/PT.
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0

Data cut as of July 01, 2019 Source: Data Package 3 Table SVII.4.6

From the last cenobamate PSUSA/00010921/202303 PRAC recommendation assessment report dated 26OCT2023, in the post-marketing period a total of 55 ICSRs (including some duplicates) relating to suicidality and in which cenobamate was (one of the) suspect(s) were retrieved from EudraVigilance. The search was performed with the HGLT “Suicidal and self-injurious behaviours NEC” and the DLP was 26 March 2023.

Among these 55 ICSRs, 11 cases with positive de-challenge were assessed as likely related to the use of cenobamate and according to the PRAC represent sufficient evidence that a causal association between the use of cenobamate and the onset of suicidal ideation is “at least at reasonable possible” as requested by the SmPC Guideline (2009 – Rev. 2).

Risk factors and risk groups:

Important risk factors identified for suicidality in general for people with epilepsy are prior or current psychiatric history and family psychiatric history.

Preventability:

The risk of suicidality with AEDs is well known and it is reasonable to assume that prescribers will be familiar with the management of this complication of treatment with AEDs. The risk will be managed in clinical practice through routine risk minimisation measures in line with the risk management plans available for other medications.

The Ontozry SmPC stipulates the class wording established for other AEDs in the EU. Healthcare professionals are informed of the risk and advised that patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Impact on the risk-benefit balance of the product:

There is a high unmet medical need for new AEDs that can produce seizure freedom. Many patients continue to experience a diminished quality of life while receiving existing therapies because the currently available drugs fail to adequately control their seizures. Cenobamate is efficacious at reducing the frequency of focal-onset seizure and increasing the rate of seizure freedom.

AEDs, as a class of medications, have been associated with an increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for cenobamate. It is generally agreed that AED treatment should not be withheld, as the risk of seizures through inadequately treated epilepsy is thought to be worse (Mula 2013). The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of suicidality that is recognised to occur with AEDs and can be managed in clinical practice.

Public health impact:

Suicidality has been associated with AEDs and the available data do not exclude the possibility of an increased risk for cenobamate. The public health impact of suicidality with cenobamate is considered to be low given that drug resistant epilepsy occurs in 12-25% of patients with epilepsy (Module SI), and that suicidality, a recognised risk for epileptic patients and with other AEDs, can be managed in clinical practice should it occur through patient monitoring.

Important potential risk 1: Hypersensitivity

Potential mechanisms:

Antiepileptic drugs can cause severe hypersensitivity reactions in a small proportion of treated individuals. The mechanism of hypersensitivity reactions associated with cenobamate is unknown.

Evidence source and strength of evidence:

In double-blind, placebo-controlled trials, 4 (0.9%) cenobamate treated patients and 1 (0.5%) placebo patient experienced hypersensitivity reaction.

For the 4 cenobamate patients, 2 experienced events of drug hypersensitivity, 1 experienced an event of hypersensitivity and 1 experienced an event on eyelid oedema. The placebo patient experienced an event of hypersensitivity. All events were classified as mild or moderate severity; there were no other severe adverse events indicative of systemic hypersensitivity other than DRESS.

Overall, the rate of hypersensitivity observed in the clinical studies was low and the cases were not severe. However, given the risk of DRESS, it was considered to also include hypersensitivity as an important potential risk of cenobamate.

Characterisation of the risk:

Hypersensitivity was identified using the customised MedDRA query (CMQ) that included the following preferred terms (PTs): hypersensitivity, drug hypersensitivity and eyelid oedema.

In the long-term open label studies (Phase 2/3 Pool), 13 patients (0.7%) (95% CI 0.4, 1.1) treated with cenobamate reported hypersensitivity (Table Part II.14). The majority of the hypersensitivity TEAEs were from the Immune system disorders SOC (n=11, 0.6%) including drug hypersensitivity (n=5, 0.3%) and hypersensitivity (n=6, 0.3%) with a small number of Eye disorders TEAEs (eyelid oedema n=2, 0.1%)(Table Part II.15).

Overall, the majority of hypersensitivity TEAEs that were reported with patients treated with cenobamate in the Phase 2/3 Pool were non-serious and of mild or moderate severity. Of the 13 patients (0.7%) treated with cenobamate with hypersensitivity this included 7 (0.4%) of mild severity and 6 (0.3%) of moderate severity (Table Part II.15). No severe hypersensitivity TEAEs were reported.

Only a patient (0.1%) treated with cenobamate reported a serious TEAE of drug hypersensitivity of moderate severity (n=1, 0.1%) (Table Part II.15). In this case, considered related to cenobamate per the investigator's assessment, the patient ([PPD]) experienced drug hypersensitivity after 1 day of cenobamate treatment (Data Package 3 Listing SVII.3.9all23). Cenobamate treatment was withdrawn and the patient recovered.

Table Part II.14 - Incidence of Combined Hypersensitivity TEAEs - All Phase 2/3 Pool

Important potential risk	Statistics	Overall Cenobamate (N = 1945) n (%) (95% CI)
Combined Hypersensitivity	n (%) (95% CI)	13 (0.7%) (0.4, 1.1)
MedDRA System Organ Class (SOC) Preferred Term (PT)		Overall Cenobamate (N = 1945) n (%)

Subjects with any Combined Hypersensitivity TEAE	13 (0.7%)
Eye disorders	2 (0.1%)
Eyelid oedema	2 (0.1%)
Immune system disorders	11 (0.6%)
Drug hypersensitivity	5 (0.3%)
Hypersensitivity	6 (0.3%)

Abbreviations: MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
n under each risk refers to the number of subjects to the concerned risk. Subjects with multiple events under the same risk is counted only once under the corresponding risk.
95% CI of % based on exact binomial distribution.
Subjects who experienced multiple events within a SOC or PT are counted once at the highest severity for that SOC/PT.
MedDRA preferred terms included within the Combined Hypersensitivity group are: Hypersensitivity, Drug hypersensitivity and Eyelid oedema
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of June 01, 2020. Source: Data Package 3 Table SVII.1.1.1 and Data Package 3 Table SVII.3.8all23

Table Part II.15 - Incidence of Combined Hypersensitivity TEAEs (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity - All Phase 2/3 Pool

MedDRA System Organ Class (SOC) Preferred Term (PT)	Overall Cenobamate (N = 1945) All TEAEs n (%)	Overall Cenobamate (N = 1945) Serious TEAEs n (%)	Overall Cenobamate (N = 1945) Non-serious TEAEs n (%)
Subjects with any Combined Hypersensitivity TEAE	13 (0.7%)	1 (0.1%)	12 (0.6%)
Mild	7 (0.4%)	0 (0.0%)	7 (0.4%)
Moderate	6 (0.3%)	1 (0.1%)	5 (0.3%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye disorders	2 (0.1%)	-	2 (0.1%)
Mild	0 (0.0%)	-	0 (0.0%)
Moderate	2 (0.1%)	-	2 (0.1%)
Severe	0 (0.0%)	-	0 (0.0%)
Eyelid oedema	2 (0.1%)	-	2 (0.1%)
Mild	0 (0.0%)	-	0 (0.0%)
Moderate	2 (0.1%)	-	2 (0.1%)
Severe	0 (0.0%)	-	0 (0.0%)
Immune system disorders	11 (0.6%)	1 (0.1%)	10 (0.5%)
Mild	7 (0.4%)	0 (0.0%)	7 (0.4%)
Moderate	4 (0.2%)	1 (0.1%)	3 (0.2%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug hypersensitivity	5 (0.3%)	1 (0.1%)	4 (0.2%)
Mild	3 (0.2%)	0 (0.0%)	3 (0.2%)
Moderate	2 (0.1%)	1 (0.1%)	1 (0.1%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hypersensitivity	6 (0.3%)	-	6 (0.3%)
Mild	4 (0.2%)	-	4 (0.2%)
Moderate	2 (0.1%)	-	2 (0.1%)
Severe	0 (0.0%)	-	0 (0.0%)

Abbreviations: MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
A subject experiencing multiple serious TEAEs of the same SOC/PT/severity will be counted only once within that corresponding SOC/PT/severity.
Subjects who experienced multiple events within a SOC or PT are counted once at the highest severity for that SOC/PT.
MedDRA preferred terms included within the Combined Hypersensitivity group are: Hypersensitivity, Drug hypersensitivity and Eyelid oedema

Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of June 01, 2020. Source: Data Package 3 Table SVII.3.9all23 and Data Package 3 Table SVII.3.3

Hypersensitivity was assessed in the double-blinded pooled dataset where the overall frequency of skin reactions was comparable for patients treated with cenobamate (Overall Cenobamate Group N = 442) N=4 (0.9%) (95% CI 0.2, 2.3) and those receiving placebo N=1 (0.5%) (95% CI 0.0, 2.6) (Table Part II.16). The majority of the skin reactions TEAEs in the Overall Cenobamate Group were from the Immune system disorders SOC (n=3, 0.7%) including drug hypersensitivity (n=3, 0.5%) and hypersensitivity (n=1, 0.2%), and there was 1 Eye disorders TEAE (eyelid oedema n=1, 0.2%).

Overall, the majority of hypersensitivity TEAEs that were reported with patients treated with cenobamate (Overall Cenobamate Group N = 442) in the Double-blind Pool were non-serious and of mild or moderate severity (Table Part II.17). Of the 4 patients (0.9%) treated with cenobamate with hypersensitivity this included 1 (0.2%) of mild severity and 3 (0.7%) of moderate severity (Table Part II.17). No severe hypersensitivity TEAEs were reported.

Only a patient (0.2%) treated with cenobamate reported a serious TEAE of drug hypersensitivity of moderate severity (n=1, 0.2%) (Table Part II.17). In this case, considered related to cenobamate per the investigator's assessment, the patient ([PPD]) experienced drug hypersensitivity after 1 day of cenobamate treatment (Data Package 3 Listing SVII.3.9). Cenobamate treatment was withdrawn and the patient recovered. No serious skin reaction TEAEs were reported in patients treated with placebo. The patient treated with placebo experienced a non-serious hypersensitivity TEAE that was of mild severity (n=1, 0.5%) (Table Part II.17).

The occurrence of hypersensitivity reactions did not increase with dose; Cenobamate 100 mg: n=2 (2.8%), Cenobamate 200 mg: n=1 (0.4%), and (Cenobamate 400 mg: n=0 (0.0%) (Table Part II.16).

There were no other severe adverse events indicative of systemic hypersensitivity other than DRESS which is classified as a separate important identified risk.

Table Part II.16 – Incidence of Combined Hypersensitivity TEAEs – Double-blind pool

Important potential risk	Statistics	Overall Cenobamate (N = 442)	Cenobamate 100 mg (N = 108)	Cenobamate 200 mg (N = 223)	Cenobamate 400 mg (N = 111)	Placebo (N = 216)
Combined Hypersensitivity	n (%)	4 (0.9%)	3 (2.8%)	1 (0.4%)	0 (0.0%)	1 (0.5%)
	95% CI	(0.2, 2.3)	(0.6, 7.9)	(0.0, 2.5)	(0.0, 3.3)	(0.0, 2.6)
	Relative risk (RR) vs Placebo	1.955	6.000	0.969	NE	
	95% CI of RR	[0.220, 17.383]	[0.632, 57.004]	[0.061, 15.388]	[NE, NE]	

MedDRA System Organ Class (SOC) Preferred Term (PT)	Overall Cenobamate (N = 442) n (%)	Cenobamate 100 mg (N = 108) n (%)	Cenobamate 200 mg (N = 223) n (%)	Cenobamate 400 mg (N = 111) n (%)	Placebo (N = 216) n (%)
Subjects with any Combined Hypersensitivity TEAE	4 (0.9%)	3 (2.8%)	1 (0.4%)	0 (0.0%)	1 (0.5%)
Eye disorders	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eyelid oedema	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Immune system disorders	3 (0.7%)	2 (1.9%)	1 (0.4%)	0 (0.0%)	1 (0.5%)
Drug hypersensitivity	2 (0.5%)	1 (0.9%)	1 (0.4%)	0 (0.0%)	0 (0.0%)
Hypersensitivity	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.5%)

Abbreviations: CI = confidence interval; MedDRA = medical dictionary for regulatory affairs; PT = preferred term; RR = relative risk; SOC = system organ class; TEAE = treatment-emergent adverse event.
n under each risk refers to the number of subjects to the concerned risk. Subjects with multiple events under the same risk is counted only once under the corresponding risk.
95% CI of % based on exact binomial distribution.
Relative risk < 1 indicates a lower risk vs placebo, and > 1 indicates a higher risk vs placebo.
A subject experiencing multiple serious TEAEs of the same SOC/PT/severity will be counted only once within that corresponding SOC/PT/severity.
MedDRA preferred terms included within the Combined Hypersensitivity group are: Hypersensitivity, Drug hypersensitivity and Eyelid oedema
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of July 01, 2019 Source: Data Package 3 Table SVII.1.2.1 and Data Package 3 Table SVII.3.8

Table Part II.17 – Incidence of Combined Hypersensitivity TEAEs (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity – Double-blind pool

	Overall Cenobamate (N = 442)			Cenobamate 100 mg (N = 108)			Cenobamate 200 mg (N = 223)			Cenobamate 400 mg (N = 111)			Placebo (N = 216)		
MedDRA System Organ Class (SOC) Preferred Term (PT)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)	All TEAEs n (%)	Serious TEAEs n (%)	Non-serious TEAEs n (%)
Subjects with any Combined Hypersensitivity TEAE	4 (0.9%)	1 (0.2%)	3 (0.7%)	3 (2.8%)	-	3 (2.8%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Moderate	3 (0.7%)	1 (0.2%)	2 (0.5%)	2 (1.9%)	-	2 (1.9%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Eye disorders	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Mild	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Moderate	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Severe	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Eyelid oedema	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Mild	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Moderate	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Severe	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Immune system disorders	3 (0.7%)	1 (0.2%)	2 (0.5%)	2 (1.9%)		2 (1.9%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	1 (0.5%)	-	1 (0.5%)
Moderate	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)

Table Part II.17 – Incidence of Combined Hypersensitivity TEAEs (All TEAEs, Serious TEAEs and Non-serious TEAEs) by severity – Double-blind pool

Drug hypersensitivit	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Mild	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Moderate	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	1 (0.4%)	1 (0.4%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	-	-	0 (0.0%)	-	-
Hypersensitivity	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	1 (0.5%)		1 (0.5%)
Mild	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	1 (0.5%)		1 (0.5%)
Moderate	1 (0.2%)	-	1 (0.2%)	1 (0.9%)	-	1 (0.9%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)
Severe	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-	-	0 (0.0%)	-	-	0 (0.0%)	-	0 (0.0%)

Abbreviations: MedDRA = medical dictionary for regulatory affairs; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
A subject experiencing multiple serious TEAEs of the same SOC/PT/severity will be counted only once within that corresponding SOC/PT/severity.
Subjects who experienced multiple events within a SOC or PT are counted once at the highest severity for that SOC/PT.
MedDRA preferred terms included within the Combined Hypersensitivity group are: Hypersensitivity, Drug hypersensitivity and Eyelid oedema
Note: Adverse Events were coded with MedDRA Dictionary Version 20.0
Data cut as of July 01, 2019. Data Package 3 Table SVII.3.9

In the post-marketing period up to 20 November 2020, there were 5 hypersensitivity spontaneous cases reported, none of which was serious. No cases of anaphylaxis or anaphylactoid reactions were reported.

Risk factors and risk groups:

Rapid titration (weekly or faster titration) of cenobamate and initiating treatment at a higher starting dose.

Preventability:

Cenobamate is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. Patients initiating treatment with cenobamate are to follow the initial dose and titration schedule as recommended in the Ontozry SmPC.

Impact on the risk-benefit balance of the product:

There is a high unmet medical need for new AEDs that can produce seizure freedom. Many patients continue to experience a diminished quality of life while receiving existing therapies because the currently available drugs fail to adequately control their seizures. Cenobamate is efficacious at reducing the frequency of focal-onset seizures in patients with treatment resistant epilepsy and increasing the rate of seizure freedom.

During the cenobamate clinical development programme the hypersensitivity reactions observed were generally non-serious and of mild or moderate severity. There were no Grade 5 skin reactions. The Ontozry SmPC contraindicates use of cenobamate in patients with hypersensitivity to the active substance or the excipients. In addition, there is comprehensive guidance for healthcare professionals concerning the recommended initial dose and titration schedule to minimise the risk of reactions including hypersensitivity.

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the risk of hypersensitivity which can be managed in clinical practice by adhering to the SmPC guidance.

Public health impact:

During the cenobamate clinical development programme there have been reports of hypersensitivity. The public health impact of hypersensitivity with cenobamate is considered to be low given that hypersensitivity occurred in <1% of patients and the reactions should they occur are likely to be of mild or moderate severity and can be managed in clinical practice.

Important potential risk 2: QT shortening

Potential mechanisms:

The mechanism by which cenobamate causes QT shortening is unknown.

Evidence source and strength of evidence:

In vitro studies found some potential for effects on the cardiovascular system.

In healthy volunteers cenobamate showed a dose-dependent shortening of the QT interval at the recommended 200 mg/day dose (Day 35) and at a supratherapeutic dose of 500 mg/day (Day 63) that were not considered clinically concerning. There is presently no substantial clinical evidence of a QT shortening non-antiarrhythmic drug increasing the risk of repolarization related arrhythmias in humans.

Characterisation of the risk:

Study C020

In Phase 1 Study C020 cenobamate showed a dose-dependent shortening of the QT interval of -11 ms for 200 mg/day and -18 ms for 500 mg/day in healthy volunteers (Table Part II.22). A higher proportion of cenobamate-treated subjects had QTcF changes from baseline of > -40 ms to <-20 ms (31% at 200 mg/day and 66% at 500 mg/day) as compared with their respective placebo groups (6-17%) (Table Part II.23).

However, no subjects had QTcF values ≤ 340 ms (calculated from Module 5.3.4.1, YKP3089C020, Appendix 16.2.9 Holter ECG dataset), and no treatment-emergent or significant atrial or ventricular arrhythmias were recorded on ECG or reported as adverse events during the double-blind treatment part of the study [C020 CSR Appendix 16.2.8.8 and Table 14.3.1.1]

Table Part II.22 – Placebo-Corrected Change from Baseline in QTcF ms (90% CI) – Study C020

	200 mg (N=51)	500 mg (N=50)
0.5 hr (max)	-10.8 (-13.4, -8.2)	-18.4 (-21.5, -15.2)
12 hr (min)	-6.3 (-8.9, -3.7)	-11.3 (-14.6, -8.1)
23.5 hr (trough)	-7.6 (-10.3, -4.9)	-14.6 (-17.9, -11.3)

Study C020 CSR, Appendix 16.2.9, Table 14.3.4-4.5.1.1

Table Part II.23 – Number (%) of Subjects with Change from Baseline QTcF Categories < -20 ms – Study 020

	N	Analysis Visit	n (%) subjects > -40 to ≤ - 20 ms	n (%) subjects ≤ - 40 ms
Cenobamate 200 mg	51	Day 35	16 (31.4)	0
Placebo	54	Day 35	3 (5.6)	0
Cenobamate 500 mg	50	Day 63	33 (66)	3 (6)
Placebo	52	Day 63	9 (17.3)	0

Source: Data Package 1 Question 124, Table 1

Pooled Double-Blind Safety Data

The magnitude of the QT shortening effect appeared to be of lesser magnitude in the double-blind trials of epilepsy patients as compared with that in healthy volunteers.

In the double-blind studies C013 and C017, ECGs were processed and interpreted by a central laboratory, and a pooled analysis assessed the mean changes from baseline in QTcF at the end of the titration period and at the end of double-blind treatment by dosing group. Except for the 400 mg cenobamate group at end of titration, there were otherwise small differences in the mean changes from baseline between the cenobamate groups and placebo (Table Part II.24).

Table Part II.24 – Mean Change from Baseline to Assessment in QTcF (ms) – Double-Blind Pool

	Cenobamate 100 mg	Cenobamate 200 mg	Cenobamate 400 mg	Placebo
End of Titration	-2.3 (N=104)	-3.0 (N=214)	-8.2 (N=107)	-0.7 (N=210)
End of Double-Blind Treatment	-2.4 (N=92)	-1.9 (N=179)	-3.7 (83)	-1.3 (N=182)

Source: ISS Appendix C, Table 9.1.1

No subjects in the cenobamate or placebo groups had absolute QTcF values <340 ms at the end of titration(Table Part II.25) or at the end of double-blind assessments (Table Part II.26). The incidence of subjects with QTcF values <360 ms was generally low and similar across cenobamate and placebo groups.

Table Part II.25 – Incidence of subjects (%) with Change from Baseline and Treatment Emergent QTcF categories, End of Titration Phase – Double-Blind Pool

	Cenobamate 100 mg N=108, NN=108	Cenobamate 200 mg N=223, NN=221	Cenobamate 400 mg N=111, NN=107	Placebo N=216, NN=209
Change from Baseline ≥ -40 to <-20 ms	6 (5.6)	24 (10.8)	14 (12.6)	12 (5.6)
Change from Baseline < -40 ms	2 (1.9)	0 (0)	2 (1.8)	1 (0.5)
QTcf <360 ms	2 (1.9)	6 (2.7)	2 (1.9)	1 (0.5)
QTcf <340 ms	0	0	0	0

N=number of subjects in the treatment group in the analysis population; NN=number of subjects in the treatment group satisfying the baseline subgroup condition.

a) Percentages are calculated using n as numerator and NN as denominator. Treatment-Emergent category is defined as a category that was not present at baseline and present as post-baseline.

Source: Data Package 1 Question 124, Table 9.2.1 and Table 9.2.1a Question 124 Table 4

Table Part II.26 – Incidence of subjects (%) with Change from Baseline and Treatment Emergent QTcf categories, Cenobamate and Placebo, End of Double-Blind Phase – Double-Blind Pool

	Cenobamate 100 mg N=108, NN=108	Cenobamate 200 mg N=223, NN=221	Cenobamate 400 mg N=111, NN=107	Placebo N=216, NN=209
Change from Baseline ≥-40 to <-20 ms	6 (5.6)	17 (7.6)	9 (8.1)	13 (6.0)
Change from Baseline <-40 ms	0 (0)	3 (1.3)	2 (1.8)	1 (0.5)
QTcf <360 ms	1 (0.9)	1 (0.5)	0	3(1.44)
QTcf <340 ms	0	0	0	0

N=number of subjects in the treatment group in the analysis population; NN=number of subjects in the treatment group satisfying the baseline subgroup condition.

a) Percentages are calculated using n as numerator and NN as denominator. Treatment-Emergent category is defined as a category that was not present at baseline and present as post-baseline.

Source: Data Package 1 Question 124, Table 9.2.1 and Table 9.2.1a Question 124 Table 5

ECG interpretation abnormalities from ECGs obtained during the double-blind treatment phase revealed no treatment-emergent clinically significant atrial or ventricular arrhythmias in any treatment group [ISS Appendix C, Table 9.3.1]. Asubject in the cenobamate 200 mg group, subject [PPD], had a non-treatment-emergent finding of atrial flutter on the day 1 ECGs which were obtained prior to 1st dose of study drug [ISS Appendix C, Table 9.3.1]. This subject also had the finding of atrial flutter reported as an adverse event, which based on the baseline ECG, would not be considered treatment-emergent [ISS Appendix E, Study YKP3089C013, [PPD]].

In the post-marketing period up to 20 November 2020, there was 1 non-serious case of supraventricular extrasystoles reported. There were no cases of QT shortening or other cardiac arrhythmias reported.

Population Studies of short QT

In a study in the Finnish population, QT intervals were measured from the 12-lead ECGs of 10,822 randomly selected middle-aged subjects enrolled in a population study and followed-up for 29 ± 10 years (Anttonen 2007). The endpoints were all-cause and cardiovascular mortality. The cutoff values for short QT intervals were defined as 320 ms (very short) and 340 ms (short). The prevalence of QT interval < 320 ms based on QTcf was 0.08% and the prevalence of QTcf < 340 ms was 0.3%. All -cause or cardiovascular mortality did not differ between subjects with a very short or short QT interval and those with normal QT intervals (360 to 450 ms). There were no sudden cardiac deaths, aborted sudden cardiac deaths, or documented ventricular tachyarrhythmias among subjects with a QTcf < 340 ms.

Another study in which the ECGs of 12,012 subjects who underwent routine medical examinations for occupational reasons were reviewed from the Medical Forensic Institute of Rome (Gallagher 2006). In the lowest ½ centile (60 subjects), the mode QTc value was 360 ms and only 6 subjects (0.05% of the study population) had QTc values < 340 ms (minimum value 335 ms). Subsequent follow-up information was available in only 36 of these subjects, and no cases of sudden death had occurred in this group at 7.9 ± 4.5 years after study entry.

Other Anti-epileptic drugs known to cause QT shortening

There are a number of drugs known to shorten or prolong the QT interval. Drugs which prolong the QT are more common and can increase the risk of Torsades de pointes (TdP) tachycardia. However, at present, no direct evidence exists of a QT shortening non-antiarrhythmic drug increasing the risk of ventricular fibrillation or other repolarization related arrhythmia (Malik 2016).

The anti-epileptic drugs lamotrigine, lacosamide and rufinamide have all been shown to shorten the QT interval. The magnitude of these effects is summarised in (Table Part II.27). Lacosamide shows dose-dependent increases in QT shortening while rufinamide shows the highest magnitude of effect with a mean change of -20 ms for doses > 2400 mg.

Table Part II.27 - Placebo-Corrected QT Shortening Effects of Anti-Epileptic Drugs, QTc (ms)

	Drug Dosage				
Lamotrigine[1]	50 BID		100 BID		200 BID
	-6.76		-4.41		-7.48
Lacosamide[2]		400 /day		800 /day	
		-4.4		-7.1	
Rufinamide[3]			> 2400 mg		
			-20		

[1]Dixon 2008, [2]Kropeit 2015, [3]Banzel US PI Question 124 Table 6

In a study of rufinamide in 19 patients with epilepsy on concomitant anti-epileptic drugs, ECGs were obtained prior to therapy and after steady state concentrations were achieved (Schimpf 2012). Patients were followed for 3.6 ± 0.67 years. Mean QTc intervals were 402 ± 22 ms before the initiation of therapy and decreased to 382 ± 16 ms after steady state (change of -20 ms). During follow-up no syncope, symptomatic cardiac arrhythmia, or cases of sudden unexpected death in epilepsy (SUDEP) were reported.

There is presently no substantial evidence of a QT shortening non-antiarrhythmic drug increasing the risk of repolarization related arrhythmias in humans.

Based on the current reviews of anti-epileptic drug induced QT shortening, the effects of cenobamate on QT are not clinically relevant and the risk of proarrhythmia by cenobamate due to a shortening of the QT is not substantiated.

Risk factors and risk groups:

The Familial Short QT Syndrome, is a very rare, inherited syndrome characterised by syncope, atrial or ventricular fibrillation and sudden death in the setting of a short QT interval as measured on a 12-lead ECG (Bjerregaard 2018). Currently there is no clinical data regarding the risks of non-antiarrhythic QT shortening drugs in this syndrome.

Preventability:

QT shortening cannot be prevented but the risk can be minimised through increased healthcare professional awareness and clinical judgement for use of cenobamate in patients with Familial Short QT Syndrome as described in the Ontozry SmPC.

Healthcare professionals are informed in the Ontozry SmPC that dose-dependent shortening of the QTcF interval has been observed with cenobamate in a placebo-controlled QT study in healthy volunteers. The mean ΔΔQTc is -10.8 [CI: -13.4, -8.2] msec for 200 mg once daily and -18.4 [CI: -21.5, -15.2] msec for 500 mg once daily (1.25 times the maximum recommended dosage). Healthcare professionals are advised that, although the underlying mechanism and safety relevance of this finding is not known, they should use clinical judgment when assessing whether to prescribe cenobamate to patients with Familial Short QT Syndrome, a rare genetic syndrome, which is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation.

Impact on the risk-benefit balance of the product:

QT data from healthy subjects in the QT Study C020 and from patients in the pooled double-blind dataset show that cenobamate is associated with dose-dependent shortening of the QTcF interval. At present, no substantive clinical evidence exists of a QT shortening non-antiarrhythmic drug increasing the risk of ventricular fibrillation or other repolarization related arrhythmia (Malik 2016). Currently there is no clinical data regarding the risks of non-antiarrhythmic QT shortening drugs in Familial QT syndrome.The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of QT shortening that is of unclear clinical significance in adult populations and can be managed in clinical practice through healthcare professional awareness and clinical judgement for use of cenobamate in patients with Familial Short QT Syndrome.

Public health impact:

The public health impact of QT shortening with cenobamate is considered to be low given that, at present, no substantive clinical evidence exists of a QT shortening non-antiarrhythmic drug increasing the risk of ventricular fibrillation or other repolarization related arrhythmia in humans.

Important potential risk 3: Reproductive/embryofoetal toxicity

Potential mechanisms:

The exact mechanism by which cenobamate causes reproductive/embryofoetal toxicity is unknown.

Evidence source and strength of evidence:

Information about using cenobamate during pregnancy is limited.

Animal studies have shown that cenobamate can affect development including decreased body weights, changes in behaviour, and how the reproductive system functions. An increase in embryo/foetal deaths was also found.

Characterisation of the risk:

There are no adequate data on the developmental risk associated with the use of cenobamate in pregnant women.

Female patients/subjects who were pregnant or lactating were excluded from enrolling in the cenobamate clinical studies. However, in total 19 cenobamate-treated patients/subjects had 20 pregnancies reported across the clinical development programme through June 2020. The outcome of the pregnancies included 7 live births (normal), 2 ectopic pregnancies, 3 spontaneous abortions, 4 elective terminations and in 3 cases the outcome was unknown (Table Part II.28).

Table Part II.28 - Pregnancy events – All studies

No.	Subject ID	Study	Age	Preferred Term	Causality	Dose mg/day	Death	SAE	Withdrawal due to AE	Outcome	Trimester(s) of exposure	Duration of exposure during pregnancy from LMP until treatment was stopped if it was
1	[PPD]	[PPD]	[PPD]	Ectopic pregnancy	Unrelated	200	No	Yes	No	Ectopic Pregnancy	1st	[PPD]. **DoE=32 days**
2	[PPD]	[PPD]	[PPD]	Fetal exposure during pregnancy	Unrelated	200	No	No	No	Live Birth (normal)	1st	[PPD]***Estimated DoE=31 days**
3	[PPD]	[PPD]	[PPD]	Pregnancy	Unrelated	200	No	Yes	No	Live Birth (normal)	1st, 2nd and 3rd	[PPD].***Estimated DoE=266 days**
4	[PPD]	[PPD]	[PPD]	Pregnancy	Unrelated	400	No	No	Yes	Elective termination	N/A	[PPD] **DoE=0**
5	[PPD]	[PPD]	[PPD]	Abortion spontaneous	Possibly	150	No	Yes	Yes	Spontaneous Abortion	1st	[PPD] **DoE was >17 days and <44 days**
6	[PPD]	[PPD]	[PPD]	Pregnancy	NA	350	No	Yes	No	Live birth (normal)	Insufficient information	[PPD]DoE potentially is throughout entire pregnancy.
7	[PPD]	[PPD]	[PPD]	Pregnancy	NA	200	No	No	No	Unknown	1st	[PPD] **DoE=37 days**
8	[PPD]	[PPD]	[PPD]	Suicide attempt/ abortion induced	Unrelated/ Not reported	350	No	Yes	No	Elective termination	Unknown	[PPD]
9	[PPD]	[PPD]	[PPD]	Pregnancy	Not reported	250	No	No	No	Elective termination	1st	[PPD] **DoE=46 days**
	[PPD]	[PPD]	[PPD]	Pregnancy	Not reported	400	No	No	No	Live birth [PPD](systemic infection)	1st, 2nd and 3rd	[PPD]. **DoE=269 days**
10	[PPD]	[PPD]	[PPD]	Abortion spontaneous	Possible	200	No	Yes	No	Spontaneous Abortion (SAE)	N/A	[PPD]**DoE=0 days**
11	[PPD]	[PPD]	[PPD]	Pregnancy	Not reported	300	No	Yes	Early termination on 20 Nov 2019 due to pregnancy	EDD: unknown No final narrative	1st	[PPD]**DoE=44 days**
12	[PPD]	C021	[PPD]	Pregnancy	NA	150	No	No	No	Elective termination (29-Oct-2019)	1st	[PPD]**DoE=39 days**

13	[PPD]	C021	[PPD]	Pregnancy	NA	400	No	Yes	Withdrew due to lack of efficacy on 29 Oct 2018	Unknown	1st	[PPD] **DoE=18 days**
14	[PPD]	C021	[PPD]	Ectopic pregnancy	Unrelated	300	No	Yes	No	Ectopic Pregnancy	1st	[PPD] **DoE=17 days.**
15	[PPD]	C021	[PPD]	Pregnancy/ Spontaneous Abortion	Unrelated	200	No	Yes	No	Abortion Spontaneous	1st	[PPD]. **DoE=38 days**
16	[PPD]	C021	[PPD]	Pregnancy	Not reported	200	No	No	No	Live birth (normal)	1st, 2nd and 3rd	[PPD]**DoE=279 days**
17	[PPD]	C021	[PPD]	Pregnancy	NA	200	No	Yes	Drug Discontinued due to pregnancy	Live birth (normal)	1st	[PPD]**DoE=18 days**
18	[PPD]	C021	[PPD]	Pregnancy	N/A	300	No	No	No	Live birth 39 weeks (normal)	1st, 2nd and 3rd	[PPD]. **DoE=282 days**
19	[PPD]	C021	[PPD]	Pregnancy	N/A	150	No	No	Drug discontinued due to pregnancy	Unknown	1st	[PPD]**DoE=35 days**

Abbreviations: c section = caesarean section; DoE = duration of exposure; EDC = estimated date of confinement; EDD = estimated delivery date; HCG = human chorionic gonadotropin; LMP = last menstrual period; N/A = not applicable

In the postmarketing period up to 20 Nov 2020, 5 [CCI/PPD] spontaneous cases of maternal exposure during pregnancy were reported, one of which also reported spontaneous abortion, as summarised below. Details are sparse in all but one case.

CIOMS [PPD]**:** This spontaneous prospective pregnancy report was received from an unknown age female patient, who experienced a maternal exposure during pregnancy (reported as pregnant) with the use of Xcopri (cenobamate). No more information was provided. Cenobamate was stopped on unknown date due to pregnancy. Additional information has been requested. The Sponsor assessed this case as unrelated to cenobamate. Maternal exposure during pregnancy is unlisted as per USPI of cenobamate.

CIOMS [PPD]**:** This spontaneous prospective pregnancy report was received from prescriber concerning an unknown age female patient, who experienced a maternal exposure during pregnancy (reported as pregnant) with the use of Xcopri (cenobamate). No more information was provided. Additional information has been requested. The Sponsor assessed this case as unrelated to cenobamate. Maternal exposure during pregnancy is unlisted as per USPI of cenobamate.

CIOMS [PPD]**:** This spontaneous prospective pregnancy report was received from a female patient of unknown age, who experienced a maternal exposure during pregnancy (reported as pregnant) and serious adverse event of abortion spontaneous (reported as miscarriage) while taking Xcopri (cenobamate). No more information was provided and was requested. The Sponsor assessed this case as unrelated to cenobamate. Maternal exposure during pregnancy and spontaneous abortion are unlisted as per USPI of cenobamate.

CIOMS [PPD]**:** A female patient of unknown age reported pregnancy while taking Xcopri (cenobamate). Medical history and concomitant medications were not reported. The patient received cenobamate, but no dispensing details were provided. Based on available information, the Sponsor assessed pregnancy as unrelated to cenobamate. Pregnancy is unlisted as per USPI of cenobamate.

CIOMS [PPD]**:** A [PPD] female patient, with a medical history of migraines, epilepsy, electrocardiogram QT prolonged, and anxiety, reported maternal exposure during pregnancy with the use of Xcopri (cenobamate). The patient was treated with cenobamate 12.5 mg daily, via an unknown route of administration on an unknown date in OCT 2020 for epilepsy or migraines (the patient was unsure about the indication). On an unknown date in OCT 2020 ([PPD]), the patient reported that she was pregnant. The time to onset was unknown but the patient reported that she had just started Xcopri and had not completed the first week of starting titration pack when she found out that she was pregnant. The patient immediately stopped medication under physician guidance on an unknown date (action taken with the cenobamate was drug withdrawn). At the time of reporting the patient is currently eight weeks and four days into her pregnancy. Based on available information, the Sponsor assessed maternal exposure during pregnancy as unrelated to cenobamate. Maternal exposure during pregnancy is unlisted as per USPI of cenobamate.

In animal studies, administration of cenobamate during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development at clinically relevant drug exposures (see Module SII). In embryo-foetal development studies in rat and rabbit, maternal toxicity was observed at high doses. In the rat, the high dose of 60 mg/kg/day resulted in increased embryo-foetal mortality, reduced foetal body weights and incomplete foetal skeletal ossification, and this was associated with maternal toxicity. There was also a small increase in visceral malformations at this high dose. However, teratogenic potential could not be fully evaluated because of the high rate of embryo-foetal deaths, which resulted in an inadequate number of foetuses examined. Therefore, the embryo-foetal study in rats showed some possible teratogenic findings at the highest dose tested. 30 mg/kg/day was the NOEL for embryo-foetal toxicity which corresponds to maternal exposure levels likely lower than the clinical exposures with the 200 and 400 mg doses.

While there was no increase in malformations in rabbits when cenobamate was administered to pregnant rabbits, the NOEL for both maternal and embryo-foetal toxicity was 12 mg/kg/day. This corresponds to maternal exposure levels well below (0.1 – 0.2-fold) clinical exposures with the 200 and 400 mg doses.

In the pre- and post-natal development study in rat, neurobehavioral impairment (increased auditory startle response) was observed in the offspring at all doses. Female offspring from high dose dams showed reproductive effects (increased early resorptions and pre- and post-implantation loss; decreased numbers of corpora lutea, implantations and live foetuses). The NOAEL for both maternal and pre- and post-natal development was 22 mg/kg/day, which corresponds to exposure levels similar to clinical exposures with the 200 mg dose but below (~ 0.5-fold) clinical exposures with the 400 mg dose.

According to the EMA post-approval commitment, a further study was performed to determine the embryo-foetal developmental toxicity and toxicokinetics, including the teratogenic potential, of cenobamate after twice daily administration to pregnant rats, in an effort to improve tolerability by decreasing C_{max} levels. Indeed, the previous study using the once daily oral dose, showed that tolerability was related to Cmax levels.

Following twice daily oral gavage administration of cenobamate to pregnant rats, C_{max} and $AUC_{0\text{-}24hr}$ values of cenobamate increased with increasing dose in an approximately dose-proportional manner on GD 6 and increased from 10 to 30 mg/kg/day in a less than dose-proportional manner with no increase from 30 to 50 mg/kg/day on GD 17. Systemic exposure (AUC0-24hr) to cenobamate did not appear to change following repeated administration of cenobamate at 10 and 30 mg/kg/day, however, exposure decreased following repeated administration of cenobamate at 50 mg/kg/day.

No cenobamate-related effects were observed on maternal survival at 10 to 30 mg/kg/day. One animal at 50 mg/kg/day was euthanized on GD 15. While the moribundity at 50 mg/kg/day was potentially cenobamate-related, all other animals (39 main study and 12 TK animals) at this dose survived to scheduled termination and therefore, not considered adverse. No cenobamate-related effects were observed on clinical findings, mean gestation body weights and body weight gain at 10 to 30 mg/kg/day or on mean gestation food consumption at 10 mg/kg/day. Non-adverse cenobamate-related findings included more frequently observed thin body condition and lower mean gestation body weights and body weight change at 50 mg/kg/day and lower mean gestation food consumption at 30 and 50 mg/kg/day. No cenobamate-related effects were observed on maternal macroscopic findings and on fetal sex ratios, body weights, or external, visceral, and skeletal examinations at any dose level evaluated.

Based upon the lack of adverse findings, in this study the NOAEL for both maternal and embryo-fetal developmental toxicity was considered to be 50 mg/kg/day. Therefore, cenobamate did not show teratogenic potential up to 50 mg/kg/day when administered to female rats during gestation.

Risk factors and risk groups:

Women of childbearing potential who are not using an effective method of contraception during cenobamate treatment are at risk of toxicity to the unborn child. In addition, women of reproductive potential concomitantly using oral contraceptives not practising an additional or alternative non-hormonal measure of birth control during treatment are at risk of toxicity to the unborn child.

Preventability:

Cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment with cenobamate. The Ontozry SmPC contains the class wording for AEDs which states that in the offspring of treated women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the

underlying condition is responsible has not been elucidated. Discontinuation of anti-epileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus.

Women of childbearing potential are advised to use effective contraception during treatment with cenobamate in the Ontozry SmPC. Women of reproductive potential concomitantly using oral contraceptives should practice additional or alternative non-hormonal measures of birth control since hormonal contraceptives are metabolised by CYP3A4 and their efficacy may be reduced by concomitant use with cenobamate.

Impact on the risk-benefit balance of the product:

The benefit of cenobamate as an effective treatment for focal-onset seizures in adult epileptic patients, who are not adequately controlled despite two AEDs, outweighs the important potential risk of reproductive/embryofoetal toxicity that can be managed in clinical practice through healthcare professional and patient awareness and use of effective contraception during treatment.

Reproductive/embryofoetal toxicity will be further characterised using EURAP - An International Registry of Antiepileptic Drugs and Pregnancy (Part III.2).

Public health impact:

There are limited data on reproductive/embryofoetal toxicity in humans but non-clinical findings suggest a potential risk to the foetus (Module SII). However, if patients with focal-onset seizures adhere to the Ontozry SmPC and avoid pregnancy the potential impact on public health is expected to be low.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table Part II.29 - Summary of safety concerns

Summary of safety concerns	
Important identified risks	Drug rash with eosinophilia and systemic symptoms (DRESS) Suicidality
Important potential risks	Hypersensitivity QT shortening Reproductive/embryofoetal toxicity
Missing information	None

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 adverse reaction follow-up questionnaire for drug rash with eosinophilia and systemic symptoms (DRESS) to further characterise the important identified risk DRESS.

Specific adverse reaction follow-up questionnaire for cardiac arrhythmia to further characterise the important potential risk QT shortening.

Other forms of routine pharmacovigilance activities: None.

III.2 Additional pharmacovigilance activities

EURAP summary

Study short name and title:

EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

Rationale and study objectives:

The primary goal is to compare the risk of major congenital malformations following maternal intake of different antiepileptic drugs and their combinations.

Secondary objectives include the evaluation of any specific pattern of foetal abnormalities, dose-effect relationships, and other risk factors.

Teratogenic endpoints of the study are the presence or absence of major malformations and prenatal growth retardation.

Evaluation of risk factors will include, among others, maternal age at conception, maternal educational level, type, dose, and administration schedule of antiepileptic drugs, type and aetiology of maternal epilepsy, onset and duration of epilepsy, type and frequency of seizures during pregnancy, other chronic or intercurrent maternal diseases, and family history of major malformations, known hereditary diseases, and epilepsy among first-degree relatives of the foetus.

Study design:

EURAP is a large prospective observational study to evaluate the outcome of pregnancies of mothers treated with antiepileptic drugs. EURAP does not interfere with the treatment prescribed by the patient's physician. 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.

Evaluations of the prevalence of teratogenic events will be based exclusively on cases followed up prospectively and enrolled before foetal outcome is known and, in any case not after the 16th week of pregnancy. Cases enrolled after birth, after the 16th week of pregnancy or after prenatal diagnosis will be reported descriptively. Follow-up continues until the infant reaches one year of age. Follow-up at one year of age may be obtained simply through a telephone interview of the mother, followed by contact with the relevant physicians if appropriate.

Information collected at specified time points include:

Enrolment:

- Study site and responsible physician(s)
- Demographics (including ethnic background and social status of parents)
- Family history (including history of epilepsy and birth defects)
- Personal history before pregnancy (including history of epilepsy and birth defects from previous pregnancies)
- Exposure to radiation before pregnancy

Follow-up for women enrolled during the first 23 weeks of gestation:

After enrolment and completion of the first trimester of pregnancy:

- Status of pregnancy and any information about foetal status
- Exposure to risk factors during first trimester of pregnancy, with special reference to alcohol, cigarette smoke, radiation, diseases
- Detailed history of exposure to drugs (including folic acid) during the first trimester of pregnancy
- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures must be obtained

After completion of the second trimester of pregnancy:

- Status of pregnancy and any information about foetal well-being
- Exposure to risk factors during second trimester of pregnancy, with special reference to alcohol, cigarette smoke, diseases
- Detailed history of exposure to drugs during the second trimester of pregnancy
- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures must be obtained

After delivery:

- Exposure to risk factors during the third trimester of pregnancy, with special reference to alcohol, cigarette smoke and diseases
- Detailed history of exposure to drugs during the third trimester of pregnancy
- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures during the third trimester of pregnancy and seizures at delivery must be obtained
- Date and site of delivery
- Obstetric complications and mode of delivery
- Clinical status of proband (Apgar score at 1 and 5 min; weight at birth, length at birth, occipital-frontal circumference)
- Detailed description of any congenital abnormality
- Post-mortem examination of proband (if applicable)

After proband completed one year of age:

- Detailed description of any congenital abnormality and time of detection
- Reasons for any hospital admission and/or surgery
- Post-mortem examination of proband (if applicable)

Follow-up for women enrolled after the first 23 weeks of gestation:

If enrolment occurs after 23 weeks of gestation but before birth, a different form will be compiled based on retrospective data and the other subforms compiled sequentially during follow-up. Each sub-form should contain the same information as outlined above for earlier enrolment.

If enrolment occurs after birth, 2 sub-forms will be compiled based on retrospective data and the other sub-forms compiled sequentially during follow-up. Each sub-form should contain the same information as outlined above for earlier enrolment.

Study population:

All women taking antiepileptic drugs at 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.

Countries participating in EURAP are from Europe, Oceania, Asia, Latin America and Africa and more than 1,500 reporting physicians from 45 countries have contributed cases to the Central Registry up to 18 June 2020 (EURAP Interim Report May 2020).

Milestones:

The EURAP publishes semi-annual reports of the progress of the project in May and November each year. Any findings of significance related to cenobamate is reported in the PSURs.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1 - Ongoing 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 *(by the competent authority)*				
Inclusion of cenobamate in EURAP - An International Registry of	EURAP's primary goal is to compare the risk of major congenital malformations following maternal intake of different AEDs, incl. cenobamate and their combinations.	Reproductive/ embryofoetal toxicity	Arvelle Therapeutics has signed an agreement to join EURAP	November 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Antiepileptic Drugs and Pregnancy Planned	Secondary objectives include the evaluation of: • any specific pattern of foetal abnormalities • dose-effect relationships • other risk factors		EURAP publishes semi-annual reports of the progress of the project twice a year that are publicly available	May and November each year
			Any findings of significance related to cenobamate will be reported in the PSURs	PSUR reports

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

There are no planned or ongoing imposed post-authorisation efficacy studies which are a condition of marketing authorisation or which are specific obligations in the context of conditional marketing authorisation or marketing authorisation under exceptional circumstances.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1 - Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk 1: Drug rash with eosinophilia and systemic symptoms (DRESS)	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance on the recommended titration schedule and that this should not be exceeded because of the potential for serious adverse reactions in SmPC Section 4.2. Warning to monitor patients for DRESS and to withdraw cenobamate immediately if signs and symptoms occur in SmPC Section 4.4. Warning that serious skin reactions including high temperature and other flu-like symptoms, rash on the face, rash spreading to other parts of the body, swollen glands, and blood tests showing increased levels of liver enzymes and of a type of white blood cell may occur in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Important identified risk 2: Suicidality	Routine risk communication: SmPC section 4.4 and 4.8 PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk Warning for patients to be monitored for signs of suicidal ideation and behaviours and to consider appropriate treatment in SmPC Section 4.4. Guidance for patients (and caregivers of patients) to be advised to seek medical advice should signs of suicidal ideation or behaviour emerge in SmPC Section 4.4. Warning for patients to talk to their doctor or pharmacist before taking Ontozry or during treatment if they have thoughts of harming or killing themselves in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Important potential risk 1: Hypersensitivity	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: Guidance on the recommended titration schedule and that this should not be exceeded because of the potential for serious adverse reactions in SmPC Section 4.2 Contraindication for patients with hypersensitivity to the active ingredient or excipients in SmPC Section 4.3 Warning for the patient not to take cenobamate if they are allergic to cenobamate or any of the other ingredients of the medicine in PL section 2 Other routine risk minimisation measures beyond the Product Information:

	Legal status: medical prescription
Important potential risk 2: QT shortening	Routine risk communication: SmPC section 5.1 Routine risk minimisation activities recommending specific clinical measures to address the risk Contraindication for Familial Short-QT syndrome in SmPC Section 4.3 Warning to use caution when prescribing cenobamate with other QT-shortening medications in SmPC Section 4.4. Contraindication in PL Section 2 for patients who were born with heart problems, with changes in the electrical activity of the heart related to a rare condition called familial short QT syndrome Warning for the patient to inform their doctor if they are taking any other medicines which they know might change the electrical activity of the heart in PL Section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription
Important potential risk 3: Reproductive/embryofoetal toxicity	Routine risk communication: SmPC sections 4.6, 5.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning that the efficacy of hormonal contraceptives may be reduced by concomitant use with cenobamate and therefore, women of reproductive potential concomitantly using oral contraceptives should use additional or alternative non-hormonal birth control in SmPC section 4.5. Warning for women of childbearing potential to use effective contraception during and 4 weeks after treatment with cenobamate and for those who are concomitantly using oral contraceptives to practice additional non-hormonal measures of birth control in SmPC section 4.6 and PL section 2. Warning that cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment with cenobamate in SmPC section 4.6. Warning for the patient to ask their doctor or pharmacist for advice before taking cenobamate if they are pregnant, think they may be pregnant, or are planning to have a baby in PL section 2. Warning for the patient to only take cenobamate during pregnancy if they and their doctor decide that it is absolutely necessary in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: medical prescription

V.2. Additional Risk Minimisation Measures

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

V.3 Summary of risk minimisation measures

Table Part V.2 - Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk 1: Drug rash with eosinophilia and	**Routine risk minimisation measures:** Warning not to exceed the titration schedule in SmPC section 4.2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
systemic symptoms (DRESS)	Warning to monitor patients closely for the signs and symptoms of DRESS in SmPC Section 4.4 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription **Additional risk minimisation measures:** None	Follow-up questionnaire for DRESS **Additional pharmacovigilance activities:** None
Important identified risk 2: Suicidality	**Routine risk minimisation measures:** Warning to monitor patients for signs of suicidal ideation and behaviours and to consider appropriate treatment in SmPC section 4.4. Guidance for patients (and caregivers of patients) to be advised to seek medical advice should signs of suicidal ideation or behaviour emerge in SmPC section 4.4 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risk 1: Hypersensitivity	**Routine risk minimisation measures:** Warning not to exceed the titration schedule in SmPC section 4.2. Contraindication for patients with hypersensitivity to the active ingredient or excipients in SmPC section 4.3 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Important potential risk 2: QT shortening	**Routine risk minimisation measures:** Contraindication for patients with Familial Short-QT syndrome in SmPC Section 4.3 Warning to use clinical judgment when assessing whether to prescribe cenobamate to patients with Familial Short QT Syndrome in SmPC Section 4.4. Contraindication for the patient not to take cenobamate in case of heart problems related to Familial Short QT Syndrome in PL Section 2. Warning for the patient to inform their doctor if they take any medicines which may change the electrical activity of the heart in PL Section 2. SmPC section 5.1	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for cardiac arrhythmia **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: medical prescription **Additional risk minimisation measures:** None	
Important potential risk 3: Reproductive/ embryofoetal toxicity	**Routine risk minimisation measures:** Warning for women of reproductive potential concomitantly using oral contraceptives to practice additional or alternative non-hormonal birth control in SmPC sections 4.5 and 4.6 and PL section 2. Warning that cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment in SmPC section 4.6 and PL section 2. SmPC section 5.3 Legal status: medical prescription **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Ontozry (cenobamate)

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

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

This summary of the RMP for Ontozry 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 Ontozry's RMP.

I. The medicine and what it is used for

Ontozry is authorised for the adjunctive treatment of focal onset seizures with or without secondary generalisation in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 anti-epileptic products (see SmPC for the full indication).

It contains cenobamate as the active substance and it is given by oral administration.

Further information about the evaluation of Ontozry’s benefits can be found in Ontozry’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <link to the EPAR summary landing page>.

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

Important risks of Ontozry, together with measures to minimise such risks and the proposed studies for learning more about Ontozry'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 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 Ontozry is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Ontozry 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 Ontozry. 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	Drug rash with eosinophilia and systemic symptoms (DRESS) Suicidality
Important potential risks	Hypersensitivity QT shortening Reproductive/embryofoetal toxicity
Missing information	None

II.B Summary of important risks

Important Identified Risk 1: DRESS	
Evidence for linking the risk to the medicine	Three cases of DRESS were seen in the clinical development of cenobamate in clinical studies with high starting doses and rapid titration. In large safety study designed to mitigate the risk of DRESS utilising a lower starting dose and slower titration scheme there were no additional cases of DRESS seen in 1340 patients.
Risk factors and risk groups	Rapid titration and initiating treatment at a higher starting dose.
Risk minimisation measures	Routine risk minimisation measures: Warning not to exceed the titration schedule in SmPC section 4.2. Warning to monitor patients closely for the signs and symptoms of DRESS in SmPC Section 4.4 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription Additional risk minimisation measures: None

Important Identified Risk 2: Suicidality	
Evidence for linking the risk to the medicine	In the pooled double-blind studies, rates of suicidal ideation and behaviours are similar for patients treated with cenobamate and placebo, and in the long-term open-label studies, for many instances of suicidal ideation or behaviour there is not enough evidence of causality based on the timing of when the patient was treated with cenobamate and when the suicidal ideation or behaviour occurred.

	While there is not enough evidence from the clinical studies that would support an increased risk for cenobamate of suicidal ideation and behaviour as patients with epilepsy have an increased risk, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic drugs (AEDs) in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, but the available data do not exclude the possibility of an increased risk for cenobamate.
Risk factors and risk groups	Important risk factors identified for suicidality in general for people with epilepsy are prior or current psychiatric history and family psychiatric history.
Risk minimisation measures	Routine risk minimisation measures: Warning to monitor patients for signs of suicidal ideation and behaviours and to consider appropriate treatment in SmPC section 4.4. Guidance for patients (and caregivers of patients) to be advised to seek medical advice should signs of suicidal ideation or behaviour emerge in SmPC section 4.4 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription Additional risk minimisation measures: None
Important Potenital Risk 1: Hypersensitivity	
Evidence for linking the risk to the medicine	In double-blind, placebo-controlled trials, 4 (0.9%) cenobamate treated patients and 1 (0.5%) placebo patient experienced hypersensitivity reaction. For the 4 cenobamate patients, 2 experienced events of drug hypersensitivity, 1 experienced an event of hypersensitivity and 1 experienced an event on eyelid oedema. The placebo patient experienced an event of hypersensitivity. All events were classified as mild or moderate severity; there were no other severe adverse events indicative of systemic hypersensitivity other than DRESS. Overall, the rate of hypersensitivity observed in the clinical studies was low and the cases were not severe. However, as hypersensitivity can be life-threatening, hypersensitivity is an important potential risk of cenobamate.
Risk factors and risk groups	Rapid titration (weekly or faster titration) of cenobamate and initiating treatment at a higher starting dose.
Risk minimisation measures	Routine risk minimisation measures: Warning not to exceed the titration schedule in SmPC section 4.2. Contraindication for patients with hypersensitivity to the active ingredient or excipients in SmPC section 4.3 and PL section 2. SmPC section 4.8 PL section 4 Legal status: medical prescription Additional risk minimisation measures: None

Important Potential Risk 2: QT shortening	
Evidence for linking the risk to the medicine	In vitro studies found some potential for effects on the cardiovascular system. In healthy volunteers cenobamate showed a dose-dependent shortening of the QT interval at the recommended 200 mg/day dose (Day 35) and at higher than the clinically recommended 500 mg/day dose (Day 63) that were not considered clinically concerning.

	There is presently no substantial evidence of a QT shortening non-antiarrhythmic drug increasing the risk of repolarization related arrhythmias in humans.
Risk factors and risk groups	Patients with Familial Short QT Syndrome, a very rare, inherited syndrome characterised by syncope, atrial or ventricular fibrillation and sudden death in the setting of a short QT interval as measured on a 12-lead ECG (Bjerregaard 2018), may be at increased risk.
Risk minimisation measures	Routine risk minimisation measures: Contraindication for patients with Familial Short-QT syndrome in SmPC Section 4.3 Warning to use clinical judgment when assessing whether to prescribe cenobamate to patients with Familial Short QT Syndrome in SmPC Section 4.4. Contraindication for the patient not to take cenobamate in case of heart problems related to Familial Short QT Syndrome in PL Section 2. Warning for the patient to inform their doctor if they take any medicines which may change the electrical activity of the heart in PL Section 2. SmPC section 5.1 Legal status: medical prescription Additional risk minimisation measures: None

Important potential risk 3: Reproductive/embryofoetal toxicity	
Evidence for linking the risk to the medicine	Information about using cenobamate during pregnancy is limited. Animal studies have shown that cenobamate can affect development including decreased body weights, changes in behaviour, and how the reproductive system functions. An increase in embryo/foetal deaths was also found.
Risk factors and risk groups	Women of childbearing potential who are not using an effective method of contraception during cenobamate treatment are at risk of toxicity to the unborn child. In addition, women of reproductive potential concomitantly using oral contraceptives not practising an additional or alternative non-hormonal measure of birth control during treatment are at risk of toxicity to the unborn child.
Risk minimisation measures	Routine risk minimisation measures: Warning for women of reproductive potential concomitantly using oral contraceptives to practice additional or alternative non-hormonal birth control in SmPC sections 4.5 and 4.6 and PL section 2. Warning that cenobamate should not be used during pregnancy unless the clinical condition of the woman requires treatment in SmPC section 4.6 and PL section 2. SmPC section 5.3 Legal status: medical prescription Additional risk minimisation measures**:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: EURAP - An International Registry of Antiepileptic Drugs and Pregnancy 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 Ontozry.

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

EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

Purpose of the study:

The primary goal is to compare the risk of major congenital malformations following maternal intake of different antiepileptic drugs and their combinations.

Secondary objectives include the evaluation of any specific pattern of foetal abnormalities, dose-effect relationships, other risk factors.

List of references in the RMP Public Summary

Bjerregaard P. Diagnosis and management of short QT syndrome. Heart Rhythm. 2018;15(8):1261-1267.

PART VII: ANNEXES

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Annex 1 – EudraVigilance Interface
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Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 Annex II: Planned and ongoing studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
EURAP - An International Registry of Antiepileptic Drugs and Pregnancy Planned *Category 3*	The primary goal is to compare the risk of major congenital malformations following maternal intake of different AEDs and their combinations. Secondary objectives include the evaluation of: • any specific pattern of foetal abnormalities • dose-effect relationships • other risk factors	Reproductive/ embryofoetal toxicity	Arvelle Therapeutics has signed an agreement to join EURAP (November 2020) EURAP publishes semi-annual reports of the progress of the project twice a year that are publicly available (May and November each year) Any findings of significance related to cenobamate will be reported in the PSURs

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
None			

Annex 3 - Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Approved protocols:

Not applicable

Final protocols not reviewed or not approved:

EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

Annex 4 - Specific adverse drug reaction follow-up forms

Drug rash with eosinophilia and systemic symptoms (DRESS) follow-up questionnaire

CENOBAMATE:
Follow-up questionnaire for Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Please complete this form and return with any supporting documentation to Arvelle Therapeutics Email: << >> If you have questions, please call us at: <<number>>

For Office use only	
Case Number	
Date received by company:	***(dd/mm/yy)***

Patient:	Male ☐
	Female ☐
Age at time of event or date of birth:	
Hospital / ID No:	

Suspect Product(s) *(add further page if required)*					
Name: CENOBAMATE		**Batch No.:**	**Indication:**		**Any cenobamate dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
Please indicate (a) Starting dose: ___ _____ **(b) Dose at which DRESS occurred: _____** **Time period between (a) and (b): _____** **(c) The titration schedule at the time of DRESS:** **_____**					
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Concomitant Medications(s) *(add further page if required)*					
Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
□ Ongoing	□ Temporarily withheld	□ Restarted	□ Dose decreased: New dose _____ mg	□ Withdrawn	

Description of DRESS including outcome:	
Start date: (dd/mm/yy)	End date (dd/yy/mm)

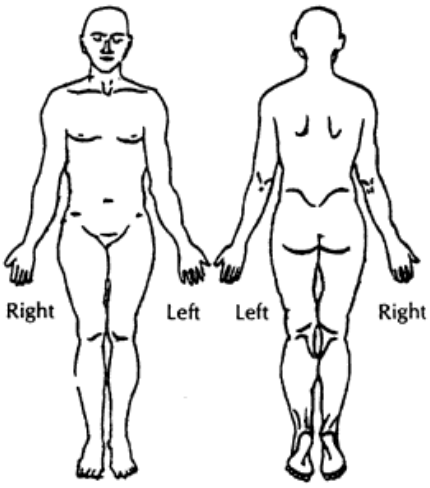
Please provide details of acute skin rash: ☐ **Yes** ☐ **No**

Details (if yes):

Start date: (dd/mm/yy)

End date: (dd/mm/yy)

Please provide % of body surface area covered by rash: _____ **%**



Please tick to show where rash is located and indicate on map.

☐ Whole body	☐ Left arm	☐ Right arm
☐ Scalp	☐ Left hand	☐ Right hand
☐ Face	☐ Left palm	☐ Right palm
☐ Chest	☐ Left foot	☐ Right foot
☐ Abdomen	☐ Left axilla	☐ Right axilla
☐ Genitalia	☐ Left sole	☐ Right sole
☐ Back		

Please indicate mucous membrane involvement ☐ Mouth ☐ Eyes ☐ Nose ☐ Genitalia

Please indicate rash appearance

☐ Macules	☐ Papules	☐ Nodules	☐ Plaques	☐ Pustules
☐ Vesicles	☐ Bullae	☐ Ulcers	☐ Urticaria	☐ Cutaneous swelling

Please provide details of facial oedema with periorbital accentuation (if applicable):

Please indicate rash symptoms

☐ Pruritus	☐ Rash pain	☐ Tenderness	☐ Epidermal necrolysis
☐ Scaling	☐ Purpura	☐ Desquamation	

Please provide skin biopsy result:

Please provide photo of skin rash and date taken if available

Please provide any relevant laboratory values below.

Laboratory values

Please provide laboratory values and reference ranges for the tests below

	Value/Date of test	Value/Date of test	Value/Date of test	Reference range
Eosinophil count				
Red blood cell count				
Haematocrit				
Haemoglobin				
White blood cell count				
Neutrophil count				
Lymphocyte count				
Monocyte count				
Differential blood count				
Atypical lymphocytes				
AST				
ALT				
Alkaline phosphatase				
Total Bilirubin				
Direct Bilirubin				
Amylase				
CPK-MM (skeletal muscle)				
CPK-MB (heart muscle)				
Plasma creatinine				
Urinary protein				
Antinuclear antibody				
Blood gases				
Blood culture				
Hepatitis A, B, C serology				
Mycoplasma/chlamydia				

Please provide details of systemic symptoms

Involvement of at least 1 internal organ: □ Yes □ No
Start date: (dd/mm/yy) End date: (dd/mm/yy)
Details (if yes):

Enlarged lymph nodes, at least 2 sites: □ Yes □ No
Start date: (dd/mm/yy) End date: (dd/mm/yy)
Details (if yes):

One of the following blood count abnormalities (values were considered abnormal if they were normal range):
Lymphocytes above or below the laboratory limits: □ Yes □ No
Start date: (dd/mm/yy) End date: (dd/mm/yy)
Details (if yes):

Eosinophils above the laboratory limits (in percentage or absolute count): □ Yes □ No
Start date: (dd/mm/yy) End date: (dd/mm/yy)
Details (if yes):

Platelets below the laboratory limits: □ Yes □ No			
Start date:	(dd/mm/yy)	End date:	(dd/mm/yy)
Details (if yes):			
Fever above 38°C: □ Yes □ No			
Start date:	(dd/mm/yy)	End date:	(dd/mm/yy)
Details (if yes):			
Abnormal chest X-Ray: □ Yes □ No			
Start date:	(dd/mm/yy)	End date:	(dd/mm/yy)
Details (if yes):			
Other, please specify: □ Yes □ No			
Start date:	(dd/mm/yy)	End date:	(dd/mm/yy)
Details (if yes):			

Management of DRESS including: (medication to treat, dose, route, duration; reaction duration,

Outcome: ☐ Recovered ☐ Recovering ☐ Not recovered ☐ Fatal

Relevant medical history such as:	☐ Allergy	☐ Previous rash	☐ Eczema
	☐ Photosensitivity	☐ Urticaria	☐ Other, please specify

Please provide any other relevant information in box below

Please use reverse and/or separate sheet for additional details

Reporting ☐doctor ☐pharmacist ☐other:	**Contact details (email or phone)**
Name:	
Address:	
Signatur	Date: (dd/mm/yy)

Cardiac arrhythmia follow-up questionnaire

CENOBAMATE:
Follow-up questionnaire for Arrhythmia
Please complete this form and return with any supporting documentation to Arvelle Therapeutics
Email: << >>
If you have questions, please call us at: <<number>>

For Office use only	
Case Number	
Date received by company:	*(dd/mm/yy)*

Patient:	Male ☐
	Female ☐
Date of birth/age at time of event:	
Hospital / ID No:	

Suspect Product(s) *(add further page if required)*					
Name: CENOBAMATE		**Batch No.:**	**Indication:**		**Any cenobamate dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
☐ Ongoing	☐ Temporarily withheld	☐ Restarted	☐ Dose decreased: New dose ____ mg	☐ Withdrawn	

Dose(s) of cenobamate over the past 1 month. Please indicate the date of interruption or discontinuation if applicable.

Suspect Product(s) *(add further page if required)*					
Name:		**Batch No.:**	**Indication:**		**Any dose changes in past 3 months? If yes, please describe below**
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency Start (dd/mm/yy)**	
Start(dd/mm/yy)	**Stop(dd/mm/yy)**				
ACTION TAKEN					
☐ Ongoing	☐ Temporarily withheld	☐ Restarted	☐ Dose decreased: New dose ____ mg	☐ Withdrawn	

Concomitant antiepileptic agents (AEDs) and doses:	Dose:
AED:	Start date:
	End date or ongoing:

Concomitant non-antiepileptic medications:	Dose:
	Start date:
	End date or ongoing:

Description of arrhythmia including symptoms and hemodynamic consequences (heart rate and blood pressure):	**Date of onset:**

Type of arrhythmia

☐ Ventricular fibrillation
☐ Ventricular tachycardia nonsustained
☐ Ventricular tachycardia sustained
☐ Torsade de Pointes
☐ Other
☐ Supraventricular tachycardia
☐ Atrial fibrillation/flutter
☐ Bradycardia (junctional rhythm)
☐ Asystole

How was the arrhythmia detected or confirmed? Please provide documentation.

☐ 12 lead ECG ☐ Holter Monitor ☐ Ambulatory continuous 12 lead ECG ☐ Telemetry monitoring ☐ Transtelephonic monitoring
☐ Other

Please provide the patient's QT, QTcF and heart rate at the time of the arrhythmia or just preceding it and please provide documentation

QT: QTcF: Heart rate:

Was heart block present?

☐ 1st degree ☐ 2nd degree ☐ 3rd degree or complete heart block

Please provide the patient's serum potassium and calcium values with their reference ranges at the time of the arrhythmia event or just preceding it.

Serum potassium: Serum calcium:

Clinical consequences and outcome

☐ Death ☐ Syncope ☐ Lightheadedness ☐ Other

Management of the arrhythmia:

☐ Medical Therapy ☐ Cardioversion ☐ Pacemaker ☐ ICD ☐ Catheter Ablation ☐ Other

Prior history of arrhythmias and treatments received:

Prior history of cardiovascular disease (please provide dates and details below):

☐ Ischemic heart disease (coronary artery disease)
☐ Myocardial infarction
☐ Chronic ischemic heart disease or angina
☐ Left ventricular dysfunction
☐ Heart failure
☐ Cardiomyopathy
☐ Other
☐ Hypertension
☐ Long QT syndrome
☐ Hypertrophic cardiomyopathy
☐ Wolf Parkinson White (WPW) syndrome
☐ Brugada syndrome
☐ Familial short QT syndrome (SQTS)

Prior history of lung disease: ☐ Chronic obstructive pulmonary disease (COPD) ☐ Asthma ☐ Other

Does the patient have:

☐ Pacemaker ☐ Implantable cardioverter defibrillator ☐ Cardiac resynchronization therapy
☐ Other cardiovascular device

Please provide any other relevant information in box below

Please use separate sheet for additional details

Reporting ☐ Doctor ☐ Pharmacist ☐ Other: ..... Name:	**Contact details (email or phone)**
..... Signatur	.....

Annex 5 - Protocols for proposed and ongoing studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities

Not applicable.

Annex 7 - Other supporting data (including referenced material)

ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration time curve
CDP	Chlordiazepoxide
CI	Confidence interval
C_{max}	Maximum plasma concentration observed
CMQ	Customised MedDRA query
CNS	Central nervous system
CrCl	Creatinine clearance
CSR	Clinical study report
CYP	Cytochrome P450
DB	Double-blind
DDD	Defined Daily Dose
DOI	2,5-Dimethoxy-4-Iodoamphetamine
DRESS	Drug reaction with eosinophilia and systemic symptoms
EC	European Community
ECG	Electrocardiogram
EEA	European Economic Area
EEG	Electroencephalogram
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GB	Great Britain
GD	Gestation Day
GLP	Good laboratory practice
hERG	human ether-à-go-go-related gene
IC_{50}	Half maximal inhibitory concentration
ILAE	International League Against Epilepsy
INN	International nonproprietary name
IV	Intravenous
MedDRA	Medical dictionary for regulatory affairs
MHRA	Medicines & Healthcare products Regulatory Agency
MTD	Maximum tolerated dose
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OECD	Organisation for economic cooperation and development
OLE	Open-label extension

PD	Pharmacodynamic
PK	Pharmacokinetic
PL	Package leaflet
PND	Post-natal day
PopPK	Population pharmacokinetic
PSUR	Periodic safety update report
PT	Preferred term
QPPV	Qualified person for pharmacovigilance
QT interval	Duration between start of Q wave and end of T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's equation
RegiSCAR	Registry of Severe Cutaneous Adverse Reactions
RMP	Risk management plan
RR	Relative risk
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
[CCI]	[CCI]
SmPC	Summary of product characteristics
SOC	System organ class
SUDEP	Sudden unexpected death in epilepsy
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TK	Toxicokinetic
UBC	United BioSource Corporation
ULN	Upper limit of normal
US	United States
USPI	US prescribing information
UV	Ultraviolet
VPA	Valproate

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Annex 8 – Summary of changes to the risk management plan over time

Version	Date of approval	Change
1.0	26MAR2021 (EC)	Not applicable
2.0 (GB-specific)	04JUN2021 (MHRA)	Change of the QPPV Removal of the wording “a history of” in Section 4.1 (Therapeutic Indication) of the GB SmPC (MHRA request)
3.0	07JUL2022	Inclusion of additional data regarding the important potential risk *Reproductive/embryofoetal toxicity*
4.0	Under evaluation	• Reclassification of the Important potential risk “Suicidality (class effect)” as an Important identified risk re-named as “Suicidality”. • Inclusion of Switzerland • Updating of post-marketing cumulative yearly exposure of patients based on European data presented in the PSUR of cenobamate dated 27NOV2023
4.1	Under evaluation	• Removal of “Confidentiality” from the footer