28 January 2021
EMA/CHMP/160820/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ontozry

International non-proprietary name: cenobamate

Procedure No. EMEA/H/C/005377/0000

Note

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

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List of abbreviations

AE	Adverse event
ADR	Adverse Drug Reaction
ASM	Antiseizure medication
ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	Body mass index
CFB	Change from baseline
CFU	Colony Forming Units
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CNS	Central nervous system
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
DB	Double-blind
DMC	Data Monitoring Committee
DRESS	Drug reaction with eosinophilia and systematic symptoms
EC	European Commission
ECG	Electrocardiogram
EDC	Electronic data capture
EU	European Union
FT-IR	Fourier Transform Infrared Spectroscopy
GABA	Gamma-aminobutyric acid
GC	Gas chromatography
GC-MS	Gas chromatography mass spectrometry
gMean	Geometric mean
GMP	Good Manufacturing Practise
HR	Heart rate
HPLC	High performance liquid chromatography
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDPE	High Density Polyethylene
HLGT	High-level group term
HLT	High-level term
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILAE	International League Against Epilepsy
IPC	In-Process Control

IPS	Intermittent photic stimulation
IR	Infrared
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention-to-Treat
KF	Karl Fischer Titration
LDPE	Low density polyethylene
LOCF	Last observation carried forward
LoD	Limit of Detection
LOQ	Limit of Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intention-to-Treat
MITT-M	Modified Intention-to-Treat, maintenance period
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
ND	Not Detected
NEC	Not elsewhere classified
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
OLE	Open-label extension
OOS	Out Of Specification
OR	Odds ratio
PAR	Proven Acceptable Range
PD	Pharmacodynamics
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PopPD	Population pharmacodynamic
PopPK	Population pharmacokinetic
FOS	Focal-onset seizure
PP	Per Protocol
PT	Preferred term
PVC	Polyvinyl chloride
QbD	Quality by Design
QC	Quality Control
QOLIE-31-P	Quality of Life in Epilepsy-Questionnaire
QTcB	QT interval corrected for heart rate using Bazett’s formula
QTcF	QT interval corrected for heart rate using Fridericia’s formula
QTTP	Quality target product profile
RegiSCAR	Registry of Severe Cutaneous Adverse Reactions
RH	Relative Humidity
ROW	Rest of the world
RRT	Relative retention time
SAE	Serious adverse event
SCB	Sodium channel blocker
SCE	Summary of clinical efficacy
SD	Standard deviation
SMPC	Summary of Product Characteristics

SOC	System organ class
SUDEP	Sudden unexpected death in epilepsy
TAMC	Total Aerobic Microbial Count
TEAE	Treatment-emergent adverse event
t_{max}	Time to achieve Cmax
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
tx	Treatment
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Arvelle Therapeutics Netherlands B.V. submitted on 9 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Ontozry, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The applicant applied for the following indication: *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.*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0120/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002563-PIP02-19 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance cenobamate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	9 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	7 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 November 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ontozry on	28 January 2021
The CHMP adopted a report on similarity of Ontozry with Epidyolex and Fintepla on	28 January 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ontozry (cenobamate) is indicated as 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.

Focal onset seizures are a group of seizures that may or may not evolve to disturbance or loss of consciousness (complex or secondary generalisation). Although the majority of patients are well controlled with 1 or 2 ASMs, over 30% of patients need new, alternative treatments as they do not gain seizure freedom on existing therapies.

2.1.2. Epidemiology

Epilepsy affects about 70 million people worldwide, making it one of the most prevalent serious neurological conditions. Each year, 16 to 134 new onset epilepsy cases per 100,000 people are diagnosed (Laxer 2014). In Europe, age-adjusted prevalence has been reported to range from 2.7 in Italy to 5.5 per 1000 in Denmark and 7.0 per 1000 in European regions of Turkey. Age-adjusted incidence of epilepsy in European studies ranged from 26 per 100,000 person-years in Norway to 47 per 100,000 person-years in England. Epilepsy has been noted to be the most common serious neurological disorder in the UK (Banerjee 2009, National Clinical Guideline Centre 2012).

2.1.3. Biologic features

Epilepsy is defined by the International League Against Epilepsy (ILAE) by any of the following conditions: (1) at least 2 unprovoked (or reflex) seizures occurring >24 h 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). Epilepsy has numerous causes, each reflecting 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 non-motor seizures with retained or impaired awareness (Fisher 2017). Focal onset seizures originate in neuronal networks limited to part of one cerebral hemisphere and may or may not secondarily generalize across the entire cortex. (Stafstrom 2015). Focal onset seizures are the most frequent form of secondary epilepsy in adults.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

People with epilepsy have a poorer overall health status, impaired intellectual and physical functioning, greater risk for accidents and injuries, and negative side effects from anti-seizure medications. They have a high rate of comorbidities, including somatic, behavioural, and psychiatric disorders. In patients with epilepsy, the prevalence of suicidal thoughts is 2–3 times higher than in those without epilepsy. Suicide appears to also be associated with chronic, drug resistant epilepsy. A recent study not only showed that seizure frequency was positively associated with suicidal tendency but also concluded that reducing seizure frequency may be the basis of suicide prevention in people with epilepsy.

The risk of premature mortality is 3 times higher in people with epilepsy than in the general population. Mortality may be due to sudden unexpected death in epilepsy (SUDEP), fatal status epilepticus, an increased risk to die of injuries such as drowning or falls, suicide, or non-psychiatric comorbidities including neoplasia and cerebrovascular and respiratory disease. Over 30% of patients need new, alternative treatments as they do not gain seizure freedom on existing therapies. Sudden unexpected death in epilepsy (SUDEP) is a leading cause of mortality among patients with epilepsy, particularly those with generalised tonic-clonic seizures. However, the greater risk of death over the general population may be reduced by achieving seizure freedom through establishing effective treatment strategies.

2.1.5. Management

Control of epilepsy primarily focuses on suppressing seizure activity because the underlying condition is not curatively treatable. Patient prognosis is generally linked to the probability to achieve seizure freedom.

Antiepileptic Drugs (ASMs) are the mainstay of epilepsy treatment. However, adverse effects of ASMs are a major source of disability, morbidity, and mortality and are a substantial burden on use and costs of health care. It is estimated that adverse effects result in early treatment discontinuation in up to 25% of patients. Cutaneous manifestations of hypersensitivity are the most common idiosyncratic reactions to ASMs and range from mild urticarioid/maculopapular eruptions to the more severe drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Despite side effect burden, the majority of patients with epilepsy have a good prognosis for full seizure control. Approximately 63% of people with epilepsy will achieve longer-term seizure freedom, and most achieve that after the first or second ASM treatment. However, over 30 % of epilepsy cases, particularly those with focal seizures, need new, alternative treatments as they do not gain seizure freedom on existing therapies. When a first drug fails, further ASMs will be initiated. 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.

Chen *et al* described that the probability of achieving seizure freedom diminishes substantially with each additional attempt at an ASM regimen. The study demonstrated that the initial ASM leads to 45.7% of patients achieving seizure freedom. If the initial ASM is ineffective, the second ASM results in an 11.6% chance of seizure freedom. Once a patient has failed a second ASM only 4.4% will achieve seizure freedom if a third regimen is required. For patients who failed 3 ASMs, only 2.1% of patients will achieved seizure control on multiple subsequent ASM regimens irrespective of the specific medications chosen.

Drug-resistant epilepsy

According to ILAE, drug-resistant epilepsy is defined as a failure of adequate trials of 2 tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom, which could be either 3 times the prior inter-seizure interval or 1 year, whichever is longer. Using the ILAE criteria, up to 44.5% of patients may be considered drug-resistant.

Patients who are refractory to drug-resistant account for most of the burden of epilepsy in the population. They experience comorbid illnesses, are at an increased risk of injury, premature death, psychological dysfunction and experience an overall reduced quality of life (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. Patients with drug-resistant epilepsy have significant neuropsychological, psychiatric, and social impairments that limit employment, reduce marriage rates, and decrease quality of life. Drug-resistant epilepsy may be progressive, carrying risks of structural damage to the brain and nervous system, comorbidities, and increased mortality, as well as psychological, educational, social, and vocational consequences. Adding to this burden is neuropsychiatric impairment caused by underlying epileptogenic processes, which seems to be independent of the effects of ongoing seizures themselves. Management of patients with drug-resistant epilepsy is particularly challenging because it is not fully understood how or why drug resistance develops in a particular patient.

Despite the availability of new ASMs with different mechanisms of action, overall outcomes in epilepsy have not improved over the last decades. While ASMs approved in the last decade demonstrate favourable PK and safety profiles; improved efficacy over first-generation ASMs has not been demonstrated in clinical studies. Zhu *et al* noted that although there was a large number of new ASMs on the market, the proportion of drug resistant patients did not change significantly. Beyenburg *et al* reported a study in which the overall weighted-pooled-risk difference in favour of ASMs over placebo for seizure-freedom in adults and children was only 6% which the authors noted was "disappointingly small". In that same analysis paper, 21% of subjects attained a 50% or greater reduction weighted-pooled-risk difference in seizure frequency in favour of ASMs over placebo. Few patients who have been assessed in adjunctive trials of ASMs developed in the past two decades become seizure free, and approximately 20% to 40% of patients show a 50% or greater reduction in the frequency of their seizures compared to 2% to 25% on placebo.

Existing treatments are not satisfactory and alternative methods are needed for those patients with epilepsy suffering from uncontrolled seizures. Because there is increasing evidence that seizure freedom will substantially reduce the burden of disease, and even mortality, in patients with epilepsy, patients who continue to have seizures should receive optimum treatment to give them the best chance of seizure freedom.

About the product

Cenobamate is a small molecule being developed as an ASM for adjunctive treatment of focal-onset seizures in patients with treatment-resistant epilepsy. It is a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel, via a binding site different from benzodiazepines. 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 mechanism of action by which cenobamate exercises its therapeutic effects remains to be fully elucidated.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 12.5 mg of cenobamate and film-coated tablets containing 25 mg, 50 mg, 100 mg, 150 mg and 200 mg of cenobamate as active substance.

Other ingredients are: lactose monohydrate, magnesium stearate (E470b), microcrystalline cellulose (E460), silica, colloidal anhydrous (E551) and sodium starch glycolate. For the film-coated tablets, the film coating consists of indigo carmine aluminium lake (E132) (only 25 mg and 100 mg), iron oxide red

(E172) (except for 50 mg), iron oxide yellow (E172), polyethylene glycol 3350, partially hydrolysed poly(vinyl alcohol) (E1203), talc (E553b) and titanium dioxide (E171).

The product is available in in a PVC blister covered with aluminium foil as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of cenobamate is [(1*R*)-1-(2-chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate corresponding to the molecular formula $C_{10}H_{10}ClN_5O_2$. It has a relative molecular mass of 267.67 and the following structure:

Figure 1

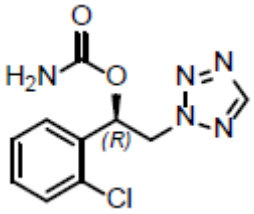


Figure 1: active substance structure

Cenobamate is a white to off-white crystalline powder which is non-hygroscopic and slightly soluble in distilled water.

Cenobamate exhibits stereoisomerism due to the presence of one chiral centre. Cenobamate is synthesised as the *R*-enantiomer.

Polymorphism has been observed for the active substance. A single polymorphic form of cenobamate is consistently produced by the manufacturing process.

Manufacture, characterisation and process controls

The active substance is synthesised in six main steps from well-defined starting materials with acceptable specifications.

During development, scientific advice was sought from two EU National Competent Authorities and both agencies agreed in the recommendation that, while the proposed starting material may be acceptable provided that specifications are tightened, the starting material should be re-defined due to the short synthetic route from the proposed starting material to the active substance and due to the fact that impurities from the proposed starting material impact on the impurity profile of the active substance.

In the MA application, the starting material was designated as initially proposed, together with tightened specification limits of impurities in the active substance. However, the CHMP did not agree with the proposed starting material as the designation was not considered fully in line with ICH Q11 and a major objection was raised. The applicant accepted to re-define the starting materials, which resolved the major objection.

Reprocessing steps are identified and sufficiently justified. Recovered or recycled solvents are not used in the process.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Benzene (class 1 as per ICH Q3C) is a potential contaminant in two solvents used in the manufacture of the active substance and an adequate control strategy has been presented for both solvents.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

During the initial assessment, the CHMP raised a major objection related to the characterisation of the active substance and the control of one nitrosamine impurity that was satisfactorily addressed by the applicant.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The critical quality attributes (CQA) and the critical process steps of the cenobamate synthesis were determined by a QbD-based risk assessment, previous knowledge, and statistical experiments.

The risk assessment is supported by knowledge of the origin and fate of the impurities.

A systematic technical review of the process parameters in the synthesis of cenobamate was performed and their proven acceptable ranges (PAR) and normal operating ranges (NOR) were determined.

The manufacturing process has been consistently reproduced with high robustness during a process validation campaign.

The proposed acceptance limits for critical process parameters (CPP) were satisfactorily justified.

Proposed holding times for intermediates are supported by stability data.

Changes introduced in the manufacturing process and the control strategy have been presented in sufficient detail and have been justified. A satisfactory summary of data and results with reference to active substance used in preclinical and clinical studies was presented.

The active substance is packaged in bags which comply with EC directive 2002/72/EC and Commission Regulation (EU) No 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (FT-IR acc. Ph. Eur., HPLC), chiral purity (HPLC), chemical purity (HPLC), impurities (HPLC), assay (HPLC), water content (KF), residue on ignition (Ph. Eur.), residual solvents (GC) and particle size distribution (laser diffraction).

Identification by IR, residue on ignition, residual solvents by GC, and particle size distribution is only tested for release of the active substance.

Proposed tests and acceptance criteria have been established based on guidelines and batch analysis data. 'In-house' specifications comply with Ph. Eur. requirements for substances for pharmaceutical use, and with ICH Q6A guidance. The proposed limits of acceptance for impurities are justified by batch analysis results and by impurity genesis and fate experimental studies. The proposed acceptance limits comply generally with requirements of current ICH guidelines Q3A, Q3C, Q3D and ICH M7. The limits proposed are supported by batch analysis and stability data and are considered acceptable.

The absence of microbiological control of the active substance was satisfactorily justified and is acceptable.

Since no significant changes have been observed in particle size distribution, a particle size test is not required in stability testing.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

A genotoxic impurity assessment has been performed, taking into account all starting materials, intermediates, reagents and reaction conditions as well as potential impurities and degradation products. Two potential impurities, both derivatives of starting material, were classified as potentially genotoxic (class 3). Two other structurally related impurities were also evaluated but classified as class 5. A detailed explanation of the origin, fate, purge and control of these potentially genotoxic impurities has been provided. The proposed acceptance criteria for these impurities have been adequately justified.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

A risk of the presence of one specific nitrosamine in cenobamate was identified based on solvents and reagents used in the route of synthesis. Updated confirmatory testing using a validated method was provided. Analytical results demonstrated that the nitrosamine is not detected. Since nitrosamines are below the 30% ICH M7 threshold for both the interim (0.24 ppm) and future limits (0.03 ppm), routine testing for the nitrosamine is not considered necessary. However, the CHMP asked for a commitment to repeat/update the confirmatory tests in batches with the redefined starting materials from the newly qualified vendors. This commitment was accepted the applicant.

Stress testing studies revealed the major degradation product of the active substance observed under all the stressed conditions. Other unknown degradation products were also observed. The stress studies performed demonstrated that the method is specific and stability indicating.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from several registration/stability batches and several validation batches (commercial scale) of active substance from the proposed manufacturer, stored in the intended commercial packaging or in a container closure system representative of that intended for the market for up to 36-60 months under long term conditions (25ºC / 60% RH) and for up to 6-12 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, identification by HPLC, assay by HPLC, chiral purity by chiral HPLC, chemical purity by HPLC, related substances by HPLC, and water content by Karl Fischer. All tested parameters were within the specification.

The analytical methods have been shown to be stability-indicating through the performance of forced degradation studies. Results from these studies under stress conditions show a considerable

degradation under extreme basic and heat conditions, and a moderate degradation under extreme oxidation and acid conditions.

No significant changes or trends were observed in any parameter at long-term (25°C), intermediate (30°C) and accelerated (40°C) storage conditions.

Photostability testing following ICH guideline Q1B was performed and showed that the active substance is not photosensitive.

The stability results justify the proposed retest period of 60 months. Any confirmed out-of-specification result, or significant negative trend, should be reported to the assessors and EMA.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release tablets, for oral administration, of six strengths: uncoated tablets (12.5 mg) and film-coated tablets (25 mg, 50 mg, 100 mg, 150 mg, and 200 mg).

The six strengths of cenobamate tablets may be differentiated by colour, size, debossing and shape (for 200 mg strength).

The composition complies with the state-of-the-art for an oral solid dosage form. The function of each excipient is explained.

The pharmaceutically and clinically relevant physicochemical properties of the active substance were duly identified, adequately specified and controlled. The chosen formulation adequately accommodates the physicochemical properties of the active substance (stability, incompatibilities, solubility, route of administration).

Throughout the re-test period the chiral purity of the active substance remained constant at 100%.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except for the film-coat material Opadry II, for which the used quantities are well justified, and an in-house standard is used. The list of excipients is included in section 6.1 of the SmPC.

Compatibility studies of active substance and several compendial excipients were performed. Cenobamate is compatible with all excipients tested.

The formulation development is supported by clinical development and details on the changes in formulation were presented.

Eventually, six tablet formulations have been developed: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg and 200 mg.

The proposed formulation is for adult and elderly patients. Because of the multiple strengths, break marks on the cenobamate tablets were not included. The statement which previously suggested that the tablets cannot be chewed or crushed has been deleted from the SmPC. The proposed dosing regimen is one (1) tablet per day until the recommended target dose of 200 mg is achieved.

Based on the critical assessment of QTPPs, the finished product specifications were established to ensure consistent quality, potency and purity of the finished product.

Pharmaceutical development studies involved the development of clinical trial material, registration tablet formulations and comprehensive scale-up studies.

The development of the dissolution test is described, and the discriminatory power of the dissolution method has been demonstrated. The method allows distinguishing changes in active substance particle size and hardness.

The physicochemical characteristic of active substance (particle size), the appropriate excipient grade, the composition of common blend and blend physical characteristic, compression profiling of tablets with different target hardness, scale up (the equipment including type of blender, coating pan, process parameters), uniform of blend flow, absence of segregation during compression were verified during development stage. Process parameter ranges are satisfactorily investigated and supported by pharmaceutical development.

The tablet manufacturing process development is described. Differences in the manufacturing processes of the commercial product and clinical trial material are adequately explained and discussed.

Comparative dissolution studies were conducted to bridge the different finished product formulations used in the early and late phase clinical studies.

The process critical parameters were identified. The process parameters used for coating were also studied. Coating parameters are determined based on the batch size, tablet load and the tablet size.

The critical process parameters (CPPs), critical material attributes (CMAs) and in-process controls (IPCs) for finished product manufacturing have been identified based on the information gained from the CPP experiments described in the section above, the data from initial formulation and process development work, clinical trial material, registration to scale-up work and general pharmaceutical manufacturing theory.

The pharmaceutical development has been properly described and includes a Quality by Design approach. The applicant presented the Quality Target Product Profile (QTTP). The quality characteristics of the product ensure the desired target product profile.

Risk assessment tools were used in to rank and select material quality attributes and /or process parameters that should be within appropriate ranges to ensure the desired product quality.

The proposed risk ranking is acceptable, and the identified risks are managed by the proposed control strategy.

The choice of materials for the container and closure is adequate to support the stability and use of the product with adults. The choice of materials for the container and closure, in particular considering their use by elderly patients, has been adequately justified.

The microbiological attributes of the finished product are those of a non-sterile solid oral dosage form complying with Ph. Eur. 5.1.4.

The primary packaging is a PCV blister covered with aluminium foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The process is considered to be a standard manufacturing process.

The 12.5 mg tablet is not coated. The 25 mg, 50 mg, 100 mg, 150 mg and 200 mg tablets are coated with a non-functional cosmetic film coat.

Process parameters and IPC were identified during development.

The acceptable process ranges were established in systematic way using QbD principles.

The proposed process validation protocols are adequate. The applicant confirms that the manufacturing process will be validated before any product is made commercially available, which is considered sufficient for this type of product and manufacturing process.

The applicant commits to conducting shipping validation under protocol.

Any post approval changes in the manufacturing process, which are beyond the approved process parameters, will be submitted and managed in compliance with the published variation guidelines.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC and UV diode array), potency assay (HPLC), related substances (HPLC), Uniformity of Dosage Unit (Ph. Eur.), water content (Ph. Eur.), dissolution (Ph. Eur.) and microbiological purity (Ph. Eur.).

In line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). A major objection was initially raised by the CHMP in relation to the nitrosamine risk assessment, but this was addressed by the applicant in a satisfactory way.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis details and data obtained with 3 batches of 12.5 mg tablets, 3 batches of 25 mg tablets, 2 batches of 50 mg tablets, 1 batch of 100 mg tablets, 2 batches of 150 mg tablets and 3 batches of 200 mg tablets. Batch sizes are also reported. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing. The testing will be conducted on the bulk tablets and no additional finished product release testing will be conducted after packaging.

Stability of the product

Stability data from registration batches of finished product, stored for up to 48 months under long term conditions (25ºC / 60% RH) and for up to 6 months for all batches under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The analytical procedures used are stability indicating. No significant changes have been observed.

Stability studies at intermediate conditions were also conducted (30°C / 65% RH).

A photostability study was conducted according with the ICH Q1B Option 2 and the data obtained demonstrate that cenobamate tablets are not photosensitive.

The proposed bulk hold time for tablets is acceptable.

The post-approval stability protocol is acceptable.

Based on available stability data, the proposed shelf-life of 48 months (4 years) for the 12.5 mg tablets, and for the 25 mg, 50 mg and 100 mg film-coated tablets and 36 months (3 years) for the 150 mg and 200 mg film-coated tablets without any special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Lactose monohydrate is the only excipient of animal origin. All other excipients used are not of human and/or animal origin. Certification from suppliers are provided indicating that no bovine spongiform encephalopathy (BSE) /transmissible spongiform encephalopathy (TSE) components are used in the manufacturing or processing of the specified excipients.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The CHMP initially raised two major objections in relation to the active substance and one major objection in relation to the finished product. The first major objection concerned the request for re-designation of the starting material. This was accepted and addressed by the applicant. The second major objection concerned the nitrosamine risk assessment and additional work needed in relation to one nitrosamine impurity. The major objection was addressed in a satisfactory way by the applicant. The third major objection also concerned the nitrosamine risk assessment and that the assessment should be extended to the container closure system and any potential external source that can contaminate the final drug product with nitrosamines. An acceptable risk assessment was provided by the applicant.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Table 1: Overview recommendations

Description
The prior contract manufacturers of YKP1941 will be removed from the dossier via a post approval variation. The drug substance manufacturing process 2.1 will be removed from the dossier via a post approval variation when the four drug substance batches made by the process 2.1 have been used. Due Date: Q2 2023
No new batches of drug substance will be manufactured by process 2.1 using the previously proposed regulatory starting materials. Any batches of the drug product, to be QP released for use after the end of Q2 2023, will contain the drug substance manufactured by process 2.2 using the newly defined regulatory starting materials. Due Date: Q2 2023
The confirmatory tests of absence of nitrosamines will be performed with batches of the pharmaceutical intermediate YKP1941 with the redefined starting materials from all the newly qualified vendors, before the release of the corresponding Drug Product batches. Due Date: Q2 2023

The above has been agreed by the applicant.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant provided an adequate non-clinical package with studies covering primary and secondary pharmacodynamics, and safety pharmacology.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Effect on $GABA_A$ channels

In vitro and *ex vivo* studies have been conducted to evaluate the effects of cenobamate on GABAergic neurotransmission.

In vitro studies demonstrated that cenobamate acts as a positive allosteric modulator of $GABA_A$ receptors and positively modulates the GABA-induced current of 6 $GABA_A$ receptor subtypes (α1β2γ2, α2β3γ2, α3β3γ2, α4β3γ2, α5β3γ2, α6β3γ2) with EC_{50} values ranging from 42 µM to 194 µM (equivalent to 11.2 to 51.9 µg/mL). Cenobamate has however limited agonist activity at these $GABA_A$ receptor subtypes (agonist EC_{50} > 1000 µM).

In rat hippocampal slices, cenobamate (300 –1,000 µM) potentiated I_{tonic} and IPSC prolongation in dentate gyrus granule cells (DGGCs). Additionally, in CA1 neurons, cenobamate at 30 –1,000 µM induced a significant I_{tonic} in a concentration-dependent manner. Despite enhancing I_{tonic}, low concentrations (30 and 100 µM) of cenobamate did not affect the amplitude and decay time of IPSCs, suggesting that while

cenobamate potentiates both synaptic (phasic) and extrasynaptic (tonic) $GABA_A$ receptors, it preferentially modulates extra-synaptic $GABA_A$Rs over their synaptic counterparts in CA1 neurons.

This assertion is strengthened by the fact that cenobamate effects were unaltered by antagonists of the benzodiazepine (BZD) receptor site, a binding site expressed by synaptic $GABA_A$Rs. At a clinically relevant concentration (~30 µM), cenobamate increased GABA-induced currents in rat hippocampal CA3 neurons, and this effect was not affected by 1 µM of the BZD antagonist flumazenil, confirming other electrophysiological and binding data that cenobamate does not exert its GABA potentiating effects through interaction with the BZD binding site.

Lack of tolerance to cenobamate anticonvulsant effects was demonstrated *in vitro* and *in vivo*. In neurons taken from rats pretreated with cenobamate at 15 mg/kg BID for 7 days, pretreatment did not affect $GABA_A$ current potentiation by cenobamate.

Effect on sodium channels

In vitro electrophysiology assays have been conducted to investigate the effects of cenobamate on Na^+ channels.

In adult rat dorsal root ganglion (DRG) neurons, cenobamate decreased the peak amplitude of tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) sodium currents in a concentration-dependent manner, suggesting that cenobamate could act on a variety of Na^+ channels.

This was subsequently confirmed by screening studies on human isoforms of Na^+ channels Nav1.1 to Nav1.8/β3 expressed in mammalian cells that showed inactivated state-dependent block by cenobamate (inactivated state IC_{50} values of the different channels ranging from 23.3 – 146 µM).

Furthermore, cenobamate potently inhibits the persistent, non-inactivating, component of I_{Na} without a significant effect on the inward transient current as demonstrated in studies in rodent hippocampal CA3 pyramidal neurons. In cultures of CA3 neurons from mice intraperitoneally-injected with pilocarpine (a model of epileptic mouse), cenobamate maintained an equally potent inhibition of voltage ramp-induced persistent Na^+ current in both saline and pilocarpine-treated mice, in contrast to carbamazepine and lacosamide that showed a reduced potency in neurons from pilocarpine-treated mice.

Cenobamate showed no significant direct interaction with receptors or voltage- or ligand-gated channels (sodium, calcium and potassium ion channels, GABA receptors, 5-hydroxytryptamine (5-HT) receptors and other receptors (adenosine A2A and A3, somatostatin sst1 and sst5, corticotropin-releasing factor [CRF1], cannabinoid CB1 and CB2, β1 adrenergic, opiate µ, tyrosine receptor kinase [Trk] A and TrkB receptors). Consequently, no single specific receptor or ion channel has been identified as being the sole contributor to the mechanism of action of cenobamate.

Anticonvulsant efficacy in rodent seizure models

Cenobamate was tested in a battery of well-characterised *in vivo* rodent seizure models:

Electrically induced seizures	
MES	• MES (maximal electroshock) is a model of generalised seizures. • ED_{50}s between 0.27 and 1.88 mg/kg PO in rats and between 7.04 and 9.84 mg/kg IP in mice. • There was no pharmacodynamic tolerance to the cenobamate anticonvulsant effect after 5 days of dosing.
6 Hz	• The 6 Hz assay is a model of therapy resistant focal seizures. • Cenobamate was equipotent at three stimulus intensities (22, 32, 44 mA) at non-toxic doses (mean ED_{50}s between 11 and 17.9 mg/kg IP), suggesting a novel mechanism of action as compared to existing ASMs. While many ASMs with different mechanisms of action are active against 22 mA induced seizures, only valproate shows equipotent efficacy at all 3 stimulus intensities.
Hippocampal kindling	• Hippocampal kindling is a model of focal onset seizures. • Cenobamate significantly inhibited seizure scores, with a mean ED_{50} of 16.4 mg/kg IP.
Chemically induced seizures	
PTZ	• Cenobamate inhibited clonic seizures induced by subcutaneous PTZ (pentylenetetrazol) in mice and rats, with ED_{50}s ranging from 3.8 to 28.5 mg/kg in multiple studies. • Cenobamate is not expected to produce any notable adverse effects on seizure threshold as doses up to 58 mg/kg IP protected against IV PTZ-induced seizure activity.
Pilocarpine	• Model of intractable seizures. • Cenobamate produced dose-dependent inhibition of seizures with an ED_{50} dose of 7 mg/kg.
Picrotoxin and Bicuculine	• Seizures are induced by these $GABA_A$ receptor antagonists. • ED_{50}s range from 23 to >70 mg/kg IP.
Genetically determined seizures	
GAERS	• GAERS (genetic absence epilepsy rat of Strasbourg) is a model of absence seizures. • Cenobamate induced a dose dependent reduction in spike wave discharges characteristic of absence seizures, with a near maximal effect at 30 mg/kg. • The effect of cenobamate appeared more prolonged than that of the reference compound valproate.

Cenobamate, administered IP and/or PO, produced antiepileptic effects in mice and rats at doses between 0.3 and 30 mg/kg.

A summary of the cenobamate effects in different seizure models in mice in comparison to other commercially available anticonvulsive drugs is presented in the following Table 2.

Table 2: Comparative Anticonvulsant Profile of Cenobamate with Selected Prototype Anticonvulsants in Mice

Test substance	Mice				
	MES	SC Met (PTZ)	SC Bic	SC Pic	6 Hz
Cenobamate	+	+	-/+	+	+
Felbamate	+	+	-	+	+
Valproate	+	+	-/+	-/+	+
Gabapentin	+	+	-	-	NT
Carbamazepine	+	-	-	-/+	-/+
Phenytoin	+	-	-	-	-/+
Lamotrigine	+	-	-	-	-/+
Topiramate	+	-	-	-	-
Levetiracetam	-	-	+	-	+
Clonazepam	-	+	+	+	+
Ethosuximide	-	+	-/+	+	+

+, Protection at doses producing no behavioural toxicity
+/-, Protection at doses producing some behavioural toxicity
-, <50% protection at highest dose tested
NT, Not tested

Secondary pharmacodynamic studies

Electrophysiological and radioligand binding studies of an extensive panel of ion channels, receptors, enzymes and transporters showed that cenobamate had no significant binding. IC_{50} values (for inhibition of radioligand binding) of 300 µM (equivalent to 80.4 µg/mL) and above for β_1 adrenergic receptor, Cl^- channel (GABA-gated), dopamine transporter, κ (KOP) and OX1 receptors were observed.

Safety pharmacology programme

A battery of safety pharmacology studies was conducted with cenobamate. The main studies and conclusions are summarised hereafter:

CNS	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. Median doses in mice and rats in tests of motor performance were much greater than those required to elicit antiepileptic effects in rodents. No evidence of epileptic seizures in an EEG study in non-human primates.
Cardiovascular	No evidence of cardiovascular effects was observed by telemetric electrocardiography in male non-human primates. *In vitro* hERG and Purkinje fiber studies indicated no prolongation of the QTc interval The Purkinje fiber study showed a small degree of action potential shortening at higher than clinically expected exposures of the drug (53% decrease in APD_{50} at 100 µM).

Respiratory	No adverse respiratory effects in the rat GLP respiratory study, except for decreased minute volume (20% of the maximum effect) at the highest dose of 60 mg/kg.
Other	Cenobamate, at 30 mg/kg, caused a moderate delay in gastrointestinal transit in the rat.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic drug interaction studies were conducted with cenobamate.

2.3.3. Pharmacokinetics

The PK/TK profile of cenobamate was evaluated across wide dose ranges in single and repeat dose studies in mice, rats, rabbits, dogs and monkeys following oral (PO), intravenous (IV), subcutaneous (SC) or intraperitoneal (IP) administration. Drug-drug interaction (DDI) potential of cenobamate was assessed *in vitro* for the most relevant cytochrome P450s, UGT enzymes and transporters.

In summary, the non-clinical ADME studies established the following:

Absorption	Cenobamate is considered highly soluble in water and highly permeable with high oral bioavailability and low clearance in mice, rats and monkeys. Primary toxicokinetic studies were conducted in rats and monkey. In rats, cenobamate exposures were generally higher in female rats than in male rats. • Exposures in males appeared dose proportional, exposures in female were less than dose-proportional. • For both genders, exposures were lower after repeated dosing compared to single dosing, indicating a potential increase in metabolism (e.g., auto-induction) after repeat dosing. In monkeys cenobamate exposures generally increased dose-proportionally in both males and females. • Exposures were generally similar or slightly higher for female monkeys. • After repeated dosing there was generally no to slight accumulation of drug for both genders.
Distribution	Protein binding data show moderate protein binding of cenobamate in animal and human plasma (43.2%, 54.9%, 35.4%, 65.0%, 60.7% to 70.7%, and 61.0% for mouse, rat, rabbit, dog, monkey and human, respectively). Evaluation of tissue distribution of [^{14}C]-cenobamate in rat show mean tissue-to-plasma ratios near 1.0 (including brain), indicating equal tissue distribution throughout the body, with the exception of higher tissue concentrations in kidney (4.7) and liver (2.7). The volume of distribution in mice, rats, dogs and monkeys was similar or slightly lower than the total body water volume, indicating that cenobamate is well distributed throughout the body.
Metabolism	Mouse, rat, rabbit and monkey showed qualitative similarities in metabolism to the human profile. • Metabolism was slow in dog, rat, monkey and human liver microsomes with dog as the fastest. • In all species, cenobamate was extensively metabolised, as evidenced by the presence of low amounts of parent drug in the excreta; ranging from 6.8% in humans to 18.5% in mice. No additional testing of metabolites was conducted as no major circulating metabolites were observed in human or nonclinical species.

	• Investigations following single oral dose administration of [^{14}C]-cenobamate showed parent drug as the major circulating radioactive component in all species. • An *ex vivo* study of human metabolism revealed presence of the parent drug (>98%) and a single N-glucuronide metabolite in human plasma, with the exposure of the N-glucuronide metabolite only 1.2% of the parent drug.
Excretion	Excretion parameters were evaluated following a single oral dose of [^{14}C]-cenobamate in mice, rats, rabbits, and monkeys. • Most of the radioactivity (≥94.0% of the dose) was excreted in urine and faeces within 168 hours for all nonclinical species. • Mice, rabbits, and monkeys excreted 70.0 to 78.8% of the dose in urine; whereas rats excreted 52.6% to 74.4% into urine. Nonclinical species generally showed similar extent of urinary excretion of cenobamate compared to humans in which 87.8% of the dose was eliminated within 312 hours.
DDI potential	Nonclinical assessments also included *in vitro* DDI studies using CYP450 enzymes, UGTs and drug transporters. • Cenobamate inhibits the metabolism enzymes CYP2B6 and CYP2C19, CYP3A4/5, UGT2B7 and UGT1A1 and the drug transporters OATP1B1, OAT3, MATE1 and MATE2-K. • In human hepatocyte assays, cenobamate induced CYP2B6, CYP2C19 and CYP3A4/5 activities, and CYP2B6, CYP2C8 and CYP3A4 mRNA levels.

2.3.4. Toxicology

Cenobamate was subjected to a complete programme of toxicity testing in multiple animal species, including single-dose and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive/developmental toxicity. Additional studies were conducted to evaluate cenobamate for abuse potential in animal models of drug dependence.

Single dose toxicity

Single dose toxicity studies were conducted in mice and rats, using the oral (gavage) and intravenous routes of administration.

Overview on single dose toxicity studies with Maximum Tolerated Dose (MTD) or No Observed Adverse Effect Level (NOAEL) values when determined.

Table 3

Study ID (GLP status)	Species	Route	Dose (mg/kg/day)	MTD or NOAEL (mg/kg)
Pharm-NJ-RG-08 (non-GLP)	CF-1 mouse	Oral	0, 100, 150 or 200	MTD = 150
1004-1175 (GLP)	CD-1 mouse	Oral	0, 10, 30, 90 or 130	NOAEL = 30
Pharm-NJ-RG-09 (non-GLP)	CF-1 mouse	Intravenous	0, 8 or 10	MTD = 8
1004-1185 (GLP)	CD-1 mouse	Intravenous	0, 1, 3, 5 or 8	NOAEL = 8
Pharm-NJ-RG-10 (non-GLP)	Sprague-Dawley rat	Oral	0, 200, 250 or 300	MTD = 200
3004-0761 (non-GLP)	Sprague-Dawley rat	Oral	150	
1004-0751 (GLP)	Sprague-Dawley rat	Oral	0, 30, 60, 100 or 150	
Pharm-NJ-RG-11 (non-GLP)	Sprague-Dawley rat	Intravenous	30 or 50	MTD approx.= 50
1004-1161 (GLP)	Sprague-Dawley rat	Intravenous	0, 1, 5, 15 or 45	NOAEL = 15

Single dose toxicity studies comprised GLP studies in mice and rats using the oral and intravenous routes of administration, each preceded by 1 or 2 non-GLP studies. GLP and non-GLP studies in mice used different animal strains (CD-1 and CF-1 mice, respectively).

In the GLP studies with oral administration, mice received doses of 0, 10, 30, 90 or 130 mg/kg/day and were observed for 8 days post-doses; rats received doses of 0, 30, 60, 100 or 150 mg/kg and were observed for 14 days. There were transient CNS toxicity at ≥ 90 mg/kg/day in mice and at all doses in rats (from 30 mg/kg/day). A NOAEL could only be set for mice, at 30 mg/kg/day. Based of extrapolation of pharmacokinetic obtained from other studies, CNS toxicity occurred with low/null safety margins for the 400 mg/day human dose. The studies indicate, therefore, a risk of acute CNS toxicity.

In the GLP studies with intravenous administration, mice received doses 0, 1, 3, 5 or 8 mg/kg and were observed for 7 days; rats received doses of 0, 1, 5, 15 or 45 mg/kg/day and were observed for 14 days. No toxicity was observed in mice. Rats showed transient CNS toxicity at 45 mg/kg. The NOAEL for mice and rats were, therefore, set at 8 and 15 mg/kg, respectively. Based on extrapolation of pharmacokinetic obtained from another study (DMPK 05-01), CNS toxicity in rats occurred with no safety margin for the 400 mg/day human dose.

No mortalities were observed in the GLP studies. In the non-GLP studies, mortalities were observed after the oral administration of 200 and ≥ 250 mg/kg to mice and rats, respectively, and intravenous administration of 10 mg/kg to mice.

Repeat dose toxicity

Repeated dose toxicity studies were conducted in mice, rats, rabbits and Cynomolgus monkeys, all using the oral (gavage) route of administration.

Table 4: Overview on repeated dose toxicity studies

Study ID (GLP status)	Species	Duration	Dose (mg/kg/day)	NOAEL (mg/kg) Major findings
SK09002 (non-GLP)	CD-1 mouse	5 days	100 or 150→50	CNS toxicity
SK09004 + SK09024 (TK) (non-GLP)	CD-1 mouse	14 days	0, 30, 60 or 120→100	60 Mortality, CNS toxicity, increase in liver weight
SK10009 (GLP)	CD-1 mouse	13 weeks	0, 10, 30, 60 or 120→90	30 Mortality, CNS toxicity, increase in liver weight, centrilobular hepatocyte hypertrophy
SK13005 (GLP)	CByB6F1 mouse	5 days and 28 days	5 days: 0, 5, 25, 50, 75 or 100 28 days: 0, 15, 35 or 75	Mortality, CNS toxicity. Liver with centrilobular hypertrophy and foci of necrosis involving clusters of hepatocytes. Hyperplasia of the non-glandular portion of the stomach.
1004-1151 (GLP)	Sprague-Dawley rat	28 days	0, 10, 30 or 100→60	30 Mortality, CNS toxicity, increase in liver weight. Hepatocellular hypertrophy and necrosis
SK07/038 (GLP)	Sprague-Dawley rat	26 week + 8-week recovery period Including 13-week interim assessment with 4-week recovery	0, 12, 24 or 48	12 Mortality, CNS toxicity, increase in liver and kidney weight. Liver with centrilobular hepatocellular hypertrophy and multifocal hepatocellular necrosis. Microscopic changes in the kidneys restricted to males.
30/022 (GLP)	New Zealand White rabbit	7 days	Phase 2 (Escalating dose phase): 25, 40, 50, 65, 80 Phase 2: 50	Mortality, CNS toxicity
1003-2053 + DMPK 2007-yc (TK) (GLP)	Cynomolgus monkey	Phase 1: single dose range finding Phase 2: 7 days	Phase 1: 10, 20, 40, 80 and 160 Phase 2: 120	Mortality, CNS toxicity
2004-0143 (non-GLP)	Cynomolgus monkey	14 days	0, 10, 30, 6040	10 CNS toxicity, increase in liver weight.
SK07/055 (GLP)	Cynomolgus monkey	Two 14 days cycles with 14 days washout	Cycle 1: 24 Cycle 2: 30	CNS toxicity

1004-0743 (GLP)	Cynomolgus monkey	28 days	0, 4, 12 or 3624	4 Mortality, CNS toxicity, emesis,
SK07/037 (GLP)	Cynomolgus monkey	52 week + 3-months recovery period Including interim assessments at 13 weeks (with and without 4 week recovery period) and at 26 weeks	13 and 26 weeks: 0, 3, 9, 18 52 weeks: 0, 9, 18, 2722	18 Mortality, CNS toxicity, increase in liver weight and minimal hepatocellular hypertrophy

→ : Reduction in dose level due to toxicity

Chronic toxicity studies included interim assessments – at 13 weeks in study in rats and at 13 and 26 weeks in the study in monkeys - and recovery periods. One of the studies in mice, which was conducted in CByB6F1 mice instead of CD-1 mice, was a dose range-finding study for a subsequent 26-week carcinogenicity study in Tg.rasH2 mice. The only study in rabbits was a dose range-finding study for subsequent preliminary toxicity study in the pregnant rabbits. One of the studies in Cynomolgus monkeys, a 7-day study, included a single escalating MTD part. Except for 5 day and 14-day studies in mice and a 14-day study in Cynomolgus monkeys, all other studies were GLP-compliant. No issues were identified which could lead to question relevance of the animal species.

In terms of toxicological findings, the longest-term study in mice (13-weeks study) showed cenobamate-related mortality and CNS toxicity at ≥60 mg/kg/day and increases in liver weight correlated microscopically to centrilobular hepatocyte hypertrophy.

In rats, the chronic toxicity study (26 weeks) showed mortality at the highest tested dose (48 mg/kg) and CNS toxicity at ≥ 24 mg/kg/day. In addition, there were changes in liver and kidneys, with increases in organs weights and histopathological changes – including centrilobular hepatocellular hypertrophy and minimal to mild multifocal hepatocellular necrosis, in the liver, and degeneration/regeneration and/or necrosis in the epithelial cells of the proximal convoluted tubules, in the kidney. All findings were reversibly upon the recovery periods.

The chronic toxicity study in Cynomolgus monkeys showed one death attributed to cenobamate and CNS toxicity at 27 mg/kg/day, a dose level which, due to toxicity, was reduced to 22 mg/kg/day from treatment Day 11 onwards. In addition, after a 52 weeks treatment (i.e. not observed at the 13 and 26 week interim assessment) there were changes in liver, with increase in liver weight at ≥ 9 mg/kg and hepatocellular hypertrophy at ≥ 18 mg/kg/day, and an increase in the incidence and severity of minimal to mild lymphoid aggregate/follicle accumulation in bone marrow and thymus at ≥ 18 and ≥ 9 mg/kg/day, respectively.

Genotoxicity

Non-mammalian Cell System: Ames Bacterial Reverse Mutation Tests (Studies No. 30/025 and No. AA30488)

Under the experimental conditions of both studies, cenobamate did not induce any biologically significant increases in the number of revertants in the 5 Salmonella typhimurium strains used, either with or without metabolic activation.

Mammalian Cell System: In Vitro Mammalian Cell Gene Mutation Test on L5178Y Mouse Lymphoma Cells TK+/- (Studies No. 30/026 and No. AA30489)

It was concluded that cenobamate did not induce mutagenic effects in the Mammalian Cell Gene Mutation Test on L5178Y Mouse Lymphoma Cells – Tk+/- either with or without metabolic activation.

Mammalian Erythrocyte Micronucleus Test in Rat Bone Marrow (Study No. 30/027)

Under the experimental conditions and according to the criteria of the study plan, it was concluded that when administered by the oral route at slightly, to very toxic dose levels of 53, 94 or 168 mg/kg, cenobamate did not induce micronuclei in rat bone marrow erythrocytes.

Carcinogenicity

26-Week Carcinogenicity and Toxicokinetic Study in Tg.rasH2 Mice (Study No. SK13035)

The objective of this GLP-compliant study was to evaluate the carcinogenic potential of cenobamate following repeated oral administration for 26 weeks in hemizygous Tg.rasH2 mice and to establish the exposure of cenobamate in wild-type CByB6F1 mice. Cenobamate at once daily oral doses of 5, 15, and 35 mg/kg/day for up to 26 consecutive weeks did not increase the incidence of neoplastic lesions. Cenobamate was considered to not to have a carcinogenic potential in the Tg.rasH2 mouse. At Week 26, the plasma concentrations of cenobamate 2 hours post-dose in male and female animals given 35 mg/kg/day were 59.5 µg/mL and 54.5 µg/mL, respectively.

104-Week Carcinogenicity and Toxicokinetic Study in Sprague-Dawley Rats (Study No. SK13015)

The objective of this GLP-compliant study was to evaluate the carcinogenic potential and TK profile of cenobamate when administered daily via oral gavage to Crl:CD (SD) rats for up to 104 weeks. No treatment related neoplastic findings were observed in male and female rats given 4, 8 or 20 mg/kg/day cenobamate via oral gavage for up to 87 and 90 weeks, respectively. No carcinogenicity potential was observed up to 20 mg/kg/day cenobamate. At the Week 26 interval, the respective exposure indices for cenobamate in plasma of male and female animals given 20 mg/kg/day were C_{max} values of 13.0 µg/mL and 20.5 µg/mL and AUC_{24} values of 173 µg*h/mL and 232 µg*h/mL.

Reproduction Toxicity

Table 5: The following reproductive and developmental toxicity studies were performed

Study type **Study ID** **GLP**	**Species (Gender)**	**Dosing period**	**Dose (mg/kg/day)**	**NOAEL (mg/kg/day)** **Major findings**
Male and female fertility and early embryonic development SK11003 (GLP)	Rat (M+F)	M: from 4 weeks prior pairing to 2-7 days after pairing F: from 2 weeks prior pairing to GD6	0, 11, 22 or 44	General tox = 44 Reprod tox = 44
Embryo-foetal development (DRF) AA26091 (non-GLP)	Rat (F)	GD 6-17	0, 20, 40 or 60	Maternal = 20 Embryo-foetal= 20 Maternal clinical signs of toxicity and weight loss. Reduction in foetal weight
Embryo-foetal development AA26092 (GLP)	Rat (F)	GD 6-17	0, 10, 30 or 60	Maternal NOEL= 10 Embryo-foetal NOEL = 30 Maternal mortality, clinical signs of toxicity, decrease on body weight and food consumption. Increase in post-implantation loss and reduction in foetal weight.
Embryo-foetal development (DRF) 30/021 (GLP)	Rabbit (F)	GD 6-19	0, 20, 30 or 40	Maternal clinical signs of toxicity, decrease in body weight and food consumption.
Embryo-foetal development 30/020 (GLP)	Rabbit (F)	GD 6-19	0, 4, 12 or 36	Maternal = 12 Embryo-foetal = 12 Maternal clinical signs of toxicity, decrease in body weight and food consumption. Slight increase in embryo-foetal death
Embryo-foetal development – TK supporting study SK15005 (GLP)	Rabbit (F)	GD 6-19	0, 4, 12 or 36	
Pre-post-natal development No. SK13019 (GLP)	Rat	GD6 – LD20	0, 11, 22 or 44	Maternal = 22 F1 = 22 Decrease in body weight and food consumption among maternal animals.

				F1 generation with effects on post-weaning functional development (males with learning and memory deficit and increased auditory startle response) and female reproductive competence.
Juvenile animals SK13034 (non-GLP)	Rat (M+F)	PND 21 - 35	0, 10, 30, 60	MTD males = 60 MTD females = 30
Juvenile animals – TK study SK14008 (GLP)	Rat (M+F)	PND 7 - 70	M: 0, 20→40, 40→80, 80→100 F: 0, 15→20, 30→60, or 60→80	
Juvenile animals SK15001 (GLP)	Rat (M+F)	PND 7 - 70	M: 0, 20→40, 30→80 or 40 →120 F: 0, 15→20, 25→50 or 35→80	M= 2040 F= 15→20 Mortality, transient decrease in body weight, reversible decrease in forelimb and hind limb grip strength and on learning and memory, changes in organ weights and histopathology.

→: Dose adjustments along study progress to increase systemic exposures

In the male and female fertility and early embryonic development study (SK11003) there were neither effects on fertility and early embryonic development nor adverse general toxicity effects. Effects observed in the parental generation were limited to adaptive liver changes, with increase in liver weight and centrilobular hepatocellular hypertrophy.

Embryo-foetal development studies in rats comprised a non-GLP dose range-finding study and a GLP pivotal study (Studies No. AA26091 and AA26092, respectively). In the pivotal study AA26092, female time-mated Sprague Dawley rats (25/dose) were dosed at 0, 10, 30 or 60 mg/kg/day on GD 6 to GD 17. There were clinical signs, mortality, and changes in body weight and food consumption among the maternal animals. There were no treatment-related macroscopic findings at the terminal necropsy examination of the maternal animals. Embryo-foetal development was affected by an increase in post-implantation loss, decrease in foetal weight and ossification. Foetal malformations were also observed. Five females given cenobamate at the dose level of 60 mg/kg/day were found dead or sacrificed in a moribund condition (between GD 10 and 19). Clinical signs prior to death or sacrifice of these females included a thin appearance, pallor, subdued behaviour, prostration, loss of balance and raised hair. Similar clinical signs were noted amongst the remaining females in the 60 mg/kg/day group. A marked treatment related weight loss occurred from GD 6 to 11 at 60 mg/kg/day and mean body weight remained relatively low through to termination. There was a transient reduction on mean body weight gain in the 30 mg/kg/day group from GD 6 to 11. Consistent with the effect on body weight, when compared with the control group, mean food consumption was reduced throughout the treatment period at 60 mg/kg/day and from GD 6 to 15 at 30 mg/kg/day. There were 25, 25, 24 and 19 pregnant females at the terminal caesarean sections in the 0, 10, 30 and 60 mg/kg/day groups, respectively. The percentage post-implantation loss was higher in the 60 mg/kg/day dose group. Foetal weight was lower

at 60 mg/kg/day. Two foetuses at 60 mg/kg/day from separate litters had anophthalmia and one foetus from each of the 30 and 60 mg/kg/day groups had enlarged ventricular chambers. It is noted that anophthalmia and heart malformations are part of the background of changes for this strain of rat at the testing facility. There was an increased incidence of foetuses with reduced ossification in several areas of the skeleton in the 60 mg/kg/day group. The findings were consistent with generalised incomplete ossification in association with the reduced foetal weight in the high dose group. The NOEL for maternal toxicity and embryo-foetal toxicity were established at 10 and 30 mg/kg/day, respectively.

In the dose range-finding study 30/021, pregnant rabbits received cenobamate at 0, 20, 30 or 40 mg/kg/day once daily from GD 6 to GD 19. The study showed maternal toxicity. Effects on embryo-foetal development were limited to a slight reduction in foetal body weight at 40 mg/kg/day.

In the pivotal study 30/020, female time-mated New Zealand White rabbits were dosed at 0, 4, 12 or 36 mg/kg/day once daily on GD 6 to GD 19. Among the maternal animals, there was no treatment related mortality or macroscopic changes at necropsy. There were clinical signs of toxicity and effects on body weight and food consumption. Embryo-foetal development was affected by a slight increase in embryo-foetal death. Changes in foetal sex ratios and foetal malformations were also observed. There were no effects in foetal body weight. The only treatment related clinical sign was an increased incidence of females with a persistent reduction in faecal output during the treatment period at 36 mg/kg/day. There was a marked reduction in overall mean body weight gain and food consumption during the treatment period in the 36 mg/kg/day group. Recovery was noted during the post-treatment period. Slight increase in in embryo-foetal death at 36 mg/kg/day. There was one foetus from the 4 mg/kg/day group with a mal-rotated hind limb. This is part of the normal background of findings for the strain of rabbit. There was no visceral foetal malformation detected in any group. There were malformed foetuses from 1, 3 and 2 litters in the 4, 12 and 36 mg/kg/day groups, respectively, with thoracic or lumber vertebral abnormalities that resulted in scoliosis for all foetuses but one. These findings were considered to be not associated with treatment. Although there was no similar finding in the concurrent control, the overall incidence of malformed foetuses (6/560: 1.1%) was less than in the historical control data (1.8% in 2002). In addition, these abnormalities are part of the normal background of findings for the strain of rabbit. The NOEL for both maternal and embryo-foetal toxicity was established at 12 mg/kg/day.

In the pre- and post-natal study (Study No. SK13019; GLP), cenobamate was well tolerated by the F0 dams. Treatment with cenobamate was not associated with mortality, effects on pregnancy or clinical signs during the gestation and lactation phases. Effects observed on F0 dams were limited to effects on body weight and food consumption. Among the F1 generation, effects were noted on body weight, post-weaning functional development and female reproductive competence. Treatment related adverse body weight loss and decreases in body weight gain were noted in females at 44 mg/kg/day from GD 6 to 9, with comparable weights to control values thereafter (including the lactation period). Transient decreased body weight gain was observed at 11 and 22 mg/kg/day on GDs 6 to 9. Additionally, treatment related decreases in food consumption at 44 mg/kg/day from GD 6 to 9 was considered adverse but transient, with slight transient decreases also observed at 11 and 22 mg/kg/day from GD 6 to 9. Among the F1 generation, slight treatment related decreases in absolute body weight and body weight gain were observed from PND 10 to 21 in males and females at 44 mg/kg/day, but were comparable to control values throughout the maturation, cohabitation, post-mating and gestation phases. Neurobehavioural impairment (learning and memory deficit and increased auditory startle response) was observed in the male offspring at all doses. Female reproductive effects at 44 mg/kg/day consisted of increases in the number of early resorptions and percent pre- and post-implantation loss, as well as decreases in the numbers of corpora lutea, implantations, and live foetuses. The maternal and F1 (pre- and post-natal development) NOAEL was established at 22 mg/kg/day.

In the pivotal juvenile animal study SK15001, there were 28 unscheduled decedents during the study among the general toxicity, reproductive toxicity, and neurohistopathology subsets. Approximately two-thirds of the deaths occurred during the dosing period from PND 8 to PND 26 and represented animals across all treated groups. The remaining unscheduled deaths occurred from PND 52 to 116. These were primarily noted in the high dose groups (males and females). In most animals, the cause of death/moribundity could not be determined. There were transient effects in body weight and body weight gain in mid and high dose males (slight, statistically significant decreases). There were cenobamate-related decreases in both forelimb and hind limb grip strength in males and females at all doses. Furthermore, during the assessment of learning and memory, at PND 61 ± 2 there were test article-related effects (increased time to complete the maze and number of errors) in high dose males in most of the learning trials and the memory recall trials. However, all effects were reversible upon discontinuation of drug. High dose males had statistically significant increases in the day of preputial separation (+1 day) and body weight (+16.8 g) at acquisition. Cenobamate-related, minimal to moderate, dose-dependent increases in liver weights were present in males and females in all dose groups. Increased liver weights correlated microscopically with centrilobular hepatocellular hypertrophy. Additionally, in males, cenobamate-related, minimal to slight, dose-dependent increases in kidney weights were present at all dose levels. Increased kidney weights correlated microscopically with renal tubular hyaline droplet accumulation. After the recovery period, all organ weight differences noted at the end of dosing had recovered. Most neurohistopathological changes that were present in the tissues examined were observed in eyes of both vehicle control and high dose animals at similar incidences. The only ocular lesion that was present at higher frequency in treated rats as compared to vehicle controls was dysplasia that involved the sclera, choroid, retinal pigmented epithelium (RPE) and retina of eyes from four high dose male animals and one vehicle control group female. These lesions were focal or multifocal, generally unilateral and were characterised by invaginations of cells through the retina that appeared to be hypertrophic and hyperplastic RPE cells with some evidence of vascular components and in some lesions a connective tissue component that was continuous with the sclera. It was considered that the nature and characteristics of the dysplastic ocular changes are consistent with a developmental origin. The NOAEL was considered to be the low dose for both males and females (20/20/30/40 and 15/15/20/20 mg/kg/day, respectively). These dose levels corresponded to C_{max} values of 9.5/9.4/12.2/17.4 µg/mL in males and 9.0/12.6/19.8/18.6 µg/mL in females, and to AUC_{24} values of 121/91.6/164/238 µg*h/mL in males and 94.9/173/284/260 µg*h/mL in females.

Local Tolerance

Since cenobamate is to be administered via oral route, no local tolerance studies were performed.

Other toxicity studies

As cenobamate is acting on the central nervous system, 5 studies were conducted to investigate the potential for drug abuse, dependence and withdrawal.

Drug Dependence and Withdrawal in Male Sprague-Dawley Rats (Study No. SK13024)

A 14-day dosing/7-day withdrawal study was run in male rats (8 animals/group). Oral doses of 0, 60 and 100 mg/kg cenobamate and 50 mg/kg BID of chlordiazepoxide (CDP) were used. Once daily dosing of cenobamate for 14 days produced only a trend towards a reduced body weight increase on Day 7, which persisted throughout the dosing and withdrawal phases. Food consumption was significantly reduced only on Day 2 of the dosing phase for animals given 60 or 100 mg/kg cenobamate. Similarly, a reduction in ambulatory and non-ambulatory activities occurred only on Day 1 of the dosing phase in

animals given 60 or 100 mg/kg cenobamate. Behavioural changes for animals given cenobamate included minimally decreased activity on Days 1 and 7 in animals given 60 mg/kg and on Days 1, 7, and 14 in animals given 100 mg/kg. In animals given 100 mg/kg, ataxia and hunched posture were noted on Days 1 and 7, respectively. During withdrawal, minimal and/or sporadic instances of slight increased activity and reactivity were noted at 60 and 100 mg/kg, and minimal instances of decreased activity were noted on Days 20 and 19 for animals given 60 or 100 mg/kg, respectively. However, most animals were normal, and the majority of observations noted were diminished by Day 20 of the withdrawal phase, indicating these effects were reversible following dosing termination.

Drug Discrimination Abuse Liability Study - Cross Generalization to Midazolam (Study No. SK13026)

The abuse liability profile of cenobamate was assessed in a drug discrimination paradigm using the BZDs midazolam and diazepam. These data indicate that animals given ≤20 mg/kg cenobamate PO did not substitute for the midazolam training cue at assessment times that ranged from 5 to 24 hours post-dose. Additionally, animals given 60 or 180 mg/kg cenobamate only exhibited partial substitution for the midazolam training cue, when tested approximately 5 hours post-dose.

Drug Discrimination: Intraperitoneal drug discrimination abuse liability potential (Study No. SK16005)

This study was conducted in male rats (16 animals/group) to examine the potential similarity of the interoceptive or subjective effects of cenobamate, to those engendered by the 1) 5HT2 (serotonin) hallucinogen, 2,5-Dimethoxy-4-iodoamphetamine (DOI); 2) dopamine agonist, stimulant, d-amphetamine; 3) mu opioid agonist, CNS depressant, morphine; 4) gamma-aminobutyric acid (GABA)benzodiazepine-Cl ionophore complex agonist, chlordiazepoxide (CDP); and 5) cannabinoid agonist, CP 55,940.

Cenobamate did not engender cross generalisation to the interoceptive stimulus properties of the selective 5HT2 agonist, DOI, or the mu opiate agonist morphine in rats trained to discriminate the presence versus absence of 0.56 mg/kg of DOI or 3.2 mg/kg morphine, respectively. Cenobamate did produce partial generalisation to the dopamine agonist, d-amphetamine, at a single dose (20 mg/kg) and a single time point (20 minutes post-dose), and a dose-dependent complete cross generalisation with 5.6 mg/kg CDP.

Self-administration potential

In order to evaluate the potential reinforcing properties of cenobamate and to assess its relative abuse liability profile, cenobamate was tested alongside the BZD midazolam, a drug with known reinforcing properties, in a self-administration study in 26 male Sprague-Dawley rats. Cenobamate produced minimal to no reinforcing behaviour over a short duration of evaluation. Infusions of cenobamate, at all doses evaluated, were significantly lower compared with midazolam. Overall, cenobamate showed a low potential for drug abuse when tested in animals trained to self-administer midazolam over a short duration of evaluation.

Study No. SK17004 (Chlordiazepoxide: Place Conditioning in Sprague-Dawley Rats) was conducted. Chordiazepoxide was however found not to be an appropriate positive control/comparator in the study.

2.3.5. Ecotoxicity/environmental risk assessment

The ERA is prepared in accordance with the EMA Guideline EMEA/CHMP/SWP/4447/00 corr 2.

Table 6: Summary of main study results

Substance (INN/Invented Name): Cenobamate			
CAS-number (if available): 913088-80-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 5 Log Dow = 1.15 pH 7 Log Dow = 1.17 pH 9 Log Dow = 1.17	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	≤3.0	
Persistence	DT50 (12°C)	From 308 to >5000 days	vP
Toxicity	NOEC	10 mg/L.	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$	2.0	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{OC} soil = 111, 164, 231 L/Kg K_{OC} sludge = 12.8 and 27.5 L/kg	No soil assessment required
Ready Biodegradability Test	OECD 301	<5% biodegradation in 28 days	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 308 to >5000 d $DT_{50,\ sediment}$ = 484 to 708 d $DT_{50,\ whole\ system}$ = 514 to 542 d %shifting to sediment >10% by day 14	DT50 at 12°C transformation products: the majority of these products accounted for less than 10 % individually

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	Growth rate and biomass NOEC	24000	µg/L	
Daphnia sp. Reproduction Test	OECD 211	Reproduction and length NOEC	11000	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	All endpoints NOEC	10000	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	64000	µg/L	
Phase IIb Studies					
Sediment dwelling organism, *Chironomus riparius*	OECD 218	NOEC (normalised to 10% Corg)	954.5	mg/kg dw	

2.3.6. Discussion on non-clinical aspects

Pharmacology

Primary pharmacology studies demonstrate that cenobamate exerts a dual mechanism of action with positive allosteric modulation of the $GABA_A$ receptors at a non-benzodiazepine binding site and enhancement of Na^+ channel inactivation along with inhibition of the persistent component of the Na^+ current.

Cenobamate produced a dose-related inhibition of hind-limb tonic-extension seizures in mice and rats subjected to the maximal electroshock seizure test, which is used to identify compounds that prevent seizure spread. There was no difference in protection between animals that had received only a single dose and those that had been treated for 5 days, suggesting no development of tolerance. In mice, cenobamate inhibited seizures in the 6 Hz corneal stimulation model, which is a model of psychomotor seizures and therapy-resistant epilepsy.

Cenobamate inhibited clonic seizures induced by pentylenetetrazol in mice and rats. These results, combined with the results of the studies of the effects of cenobamate on seizure expression and after-discharge duration in the rapid hippocampal kindling model in Sprague-Dawley rats, suggest that cenobamate does not potentiate seizure initiation and may be efficacious against focal seizures.

Cenobamate also produced a dose-dependent inhibition of seizures induced by picrotoxin or bicuculline, which provoke seizures via their antagonism of $GABA_A$ receptors. This correlates with the positive modulating effect of cenobamate on GABA-induced currents.

Cenobamate was efficacious in the GAERS rat genetic model of absence epilepsy suggesting it may be effective in treating this type of generalised seizures.

Cenobamate produced dose-dependent inhibition of seizures in rats treated with the cholinergic muscarinic agent pilocarpine (inducing sustained convulsions similar to status epilepticus) along with lithium carbonate to lower seizure threshold.

Studies to investigate secondary pharmacodynamic effects of cenobamate have centred around the effects of the drug on overall behaviour.

Cenobamate did not significantly reverse scopolamine-induced memory impairment when administered intraperitoneally. However, cenobamate was found to potentiate ethanol-induced anesthesia and hexobarbital sleeping time at doses of 30 mg/kg and above. Cenobamate did not potentiate L-5-HTP-induced head twitches thereby exhibiting neither MAO-A inhibition nor $5\text{-}HT_{2A}$ receptor agonist activity. However, cenobamate dose-dependently antagonised the DOI-induced head twitch response exhibiting $5\text{-}HT_{2A}$ receptor antagonism activity in mice.

Two non-GLP Irwin screening studies were conducted to establish the tolerability of cenobamate. The maximum tolerated dose (based on CNS signs such as decreased activity, ataxia, ptosis and loss of righting reflex) was 200 mg/kg orally in rats. A significant increase in ataxia and ptosis with decreased locomotor activity, muscle tone and motor function were also observed at 100 mg/kg.

The cardiovascular effects of cenobamate were assessed in a standard battery of *in vitro* studies as described in the ICH S7 guidelines. Cenobamate is considered to have a small risk for hERG inhibition as the IC_{50} in the hERG assay (1,869 µM) is 11-fold higher than the clinical steady state C_{max} observed after the 400 mg/day dose and 27-fold higher than the free drug plasma levels at steady state.

In isolated rabbit Purkinje fibers, cenobamate exhibits some QT interval-shortening effects at 100 µM in the rabbit, which is slightly more than the free drug plasma levels at steady state (68 µM) in human

patients at the 400 mg/day dose. The clinical significance of the QT interval shortening is further investigated and discussed in the clinical sections.

Pharmacokinetics

Cenobamate is highly soluble and highly permeable in water. Oral bioavailability of cenobamate is generally moderate to high in mice, rats and monkeys, and very low in dogs. The clearance of cenobamate is very low in mice, rats and monkeys at 1.2% to 7.3% of hepatic plasma flow whereas the clearance in dogs is high at 60% of hepatic plasma flow.

After repeated dose administrations, systemic exposures to cenobamate generally increased dose-proportionally in both male and female animals. Compared to male animals, exposures were generally similar or slightly higher for female animals. Systemic exposures in rats were lower after repeated dosing compared to single dose which correlated to potential auto-induction as indicated by increased CYP and UGT activities in *ex vivo* analyses. After repeated doses of cenobamate in monkeys, there was generally no to slight accumulation of drug.

Plasma protein binding of cenobamate was low to moderate (35-71%) in all species tested and it bound to human albumin protein (66.7%) but not to α_1-acid glycoprotein. In a rat tissue distribution study with [^{14}C]-cenobamate, most of the mean tissue-to-blood ratios were near 1.0 including brain indicating cenobamate was well distributed in the body. The kidney had the highest tissue-to-blood ratios followed by the liver. Placental transfer of cenobamate was confirmed by the presence of cenobamate in both amniotic fluid and fetal blood from pregnant rats. Even though rat breast milk was not evaluated, based on the tissue distribution data, cenobamate is likely to be present in milk.

Cenobamate was extensively metabolised as shown by the low levels of parent drug in excreta, ranging from 6.8% in humans to 18.5% in mice. N-Glucuronide (M1) represented the major clearance pathway for cenobamate in humans and monkeys. For humans, two other metabolites accounted for ≥10% of the excreted dose; M2b and the dihydrodiol metabolites combined (M6 and M7). No *in vivo* chiral inversion of cenobamate (R-enantiomer) to its S-enantiomer was observed in plasma from rats, monkeys or humans. Monkey had a similar metabolic profile as the human profile. The mouse, rat and rabbit were also confirmed to be appropriate toxicology species given the qualitative similarities in metabolism compared to the human profile where cenobamate was the major circulating component in plasma and sufficient oral absorption to produce CNS toxicity. As no major circulating metabolites (≥10% of the dose) were observed in human or nonclinical species, no additional testing of metabolites was conducted. This is agreed.

After single oral doses of [^{14}C]-cenobamate, most of the radioactivity (≥94.0% of the dose) was excreted within 168 hours for all species. Nonclinical species generally showed similar extent of urinary excretion of cenobamate compared to humans (87.8% of the dose eliminated within 312 hours).

Multiple CYP- and UGT-enzymes have been shown to be involved with the metabolism of cenobamate including UGT2B7, CYP2E1, CYP2A6 and CYP2B6. Other metabolic enzymes including UGT2B4, CYP2C19 and CYP3A4/5 may also be involved to a minor extent. Cenobamate inhibits CYP2B6 and CYP2C19 and to a lesser extent CYP3A4/5, UGT2B7 and UGT1A1.

In vitro transporter inhibition data suggests cenobamate has the potential to interact with substrates of the hepatic uptake transporter OATP1B1, and the renal uptake transporters OAT3, MATE1 and MATE2-K.

Therefore, based on these *in vitro* data and the clinically relevant inhibition of multiple CYP enzymes (CYP2B6, 2C19, and 3A) and both UGT enzymes (UGT1A1 and UGT2B7) as well as the inhibition of the drug transporters OATP1B1, OAT3, MATE1 and MATE2-K, cenobamate is predicted to cause a number of

interactions with medicinal products. This was further investigated and assessed in a pharmacokinetic study (YKP3089C026). In addition, the applicant conducted five drug-drug interactions studies and a population PK analysis to assess the effects of cenobamate on the PK of other anti-epileptic drugs (see clinical sections)

Toxicology

Cenobamate was subjected to a complete programme of toxicity testing in multiple animal species, including single-dose and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive/developmental toxicity. Additional studies were conducted to evaluate cenobamate for abuse potential in animal models of drug dependence.

Single dose toxicity studies were conducted in mice and rats, using the oral and intravenous routes of administration. Additionally, an oral single escalating MTD study was conducted in Cynomolgus monkeys. Significant clinical signs included ataxia, tremor, loss of righting reflex, immobility and decreased respiration.

Repeated dose toxicity studies were conducted in mice, rats, rabbits and Cynomolgus monkeys, using the oral route of administration. The longest-term studies in mice, rats and Cynomolgus monkeys all showed CNS toxicity, mortality, and changes in the liver comprising increase in weight and centrilobular hepatocellular hypertrophy. Additionally, rats showed hepatocellular necrosis, considered secondary to the centrilobular hepatocellular hypertrophy, and changes in kidneys without a human counterpart. Monkeys showed lymphoid aggregates in bone marrow and thymus considered to be of uncertain/limited relevance to humans. Shorter terms studies also revealed thymic atrophy and lymphoid necrosis in the thymus and lymph nodes in rats, and few dark red areas of the thymus in monkeys. Based on systemic exposures, the observed changes occurred with low or no safety margins to humans at the intended maximum clinical dose of 400 mg/day.

Cenobamate did not show genotoxicity in the 3 genotoxicity studies. Furthermore, the histopathology data from the repeat dose toxicity studies did not suggest a proliferative response to exposure to cenobamate. These results further translate into a lack of a carcinogenic potential in the 6-month Tg.rasH2 transgenic mouse and 2-year rat studies.

Reproductive and developmental toxicity studies comprised a fertility and early embryonic development study, 4 embryo-foetal development studies (including the dose-range finding studies), a prenatal and postnatal development study and 3 studies with direct dosing of the offspring. Administration of cenobamate during pre-mating, cohabitation, or gestation/post-mating phases was well-tolerated by male and female rats with no treatment related mortalities. There were no effects on oestrous cycling, male or female fertility or mating indices, sperm motility, count, and morphology, or Caesarean section parameters.

There were adverse effects on embryo-foetal development at dose levels toxic for the mothers in the embryo-foetal development studies conducted both in rats and rabbits (reduction in the number of viable foetuses, reduction in foetal body weight and ossification in rat and slight increase in foetal death in rabbits). Furthermore, in the rat study, there were 4 foetuses with visceral malformations (at 60 mg/kg/day, 2 foetuses from separate litters with anophthalmia and 1 foetus with enlarged ventricular chambers; at 30 mg/kg/day, one foetus with enlarged ventricular chambers). It was estimated that, both in rats and rabbits, systemic exposures at the NOAEL and maximum tested doses were lower than human exposure at the intended maximum clinical dose of 400 mg/day

The pre-post-natal development study conducted in rats showed transplacental passage of cenobamate and adverse effects both in the mothers and in the offspring. Effects observed among the F1 generation animals comprised lower body weights, which was transient, learning and memory deficits

and increased auditory startle response, observed in males at all doses, and a decrease in female reproductive competence at the high dose. Systemic exposures at both the NOAEL and maximum tested dose were lower than human exposure at the intended maximum clinical dose of 400 mg/day.

Due to the inadequate number of foetuses examined, no definitive conclusion could be drawn and the full teratogenic potential of cenobamate could not be established. The CHMP noted that the rat embryo-foetal development study is being repeated and the applicant will provide the study report once finalised.

Even though the observed malformations may be considered part of the background and without obvious association to treatment, the reproductive toxicity studies showed adverse effects on embryo-foetal and postnatal development occurring at lower systemic exposures than the anticipated therapeutic levels in humans. The CHMP agreed that the information, the relevant risks and recommendations, including the need to use an effective contraception during the treatment and until 4 weeks after discontinuation and – for precautionary measures - to discontinue breastfeeding during treatment are correctly reflected in sections 4.6 and 5.3 of the SmPC.

Five studies were also conducted to assess the drug abuse liability and dependence potential of cenobamate (drug discrimination, self-administration and drug dependence). Cenobamate showed a low potential for drug abuse when tested in animals trained to self-administer midazolam. It did engender partial generalisation to d-amphetamine at a single time-point and complete cross generalisation to chlordiazepoxide. Overall, cenobamate is considered to have some potential for drug abuse or dependence liability in humans and this was further investigated in the clinical aspects (see pharmacology and clinical safety discussions).

Ecotoxicity/Environmental Risk Assessment (ERA)

The Environmental Risk Assessment (ERA) for cenobamate was prepared in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use - (EMEA/CHMP/SWP/4447/00 corr 21*, 01 June 2006). Based on PEC results (≥0.01 threshold), a phase II assessment was required. Considering the available data, it can be concluded that cenobamate is not biodegradable. The ecotoxicological studies did not demonstrated expected risk to surface waters. The trigger value for adsorption to sewage sludge is not exceeded. However, the results demonstrate that cenobamate would have medium to high mobility in soils. The shifting of cenobamate to sediment was >10% by day 14, requiring a sediment effect study. The dissipation rates of cenobamate normalised to 12° showed that cenobamate is potentially very persistent (vP) in aquatic systems. No risks were identified by the calculated PEC/PNEC ratio(s) (RQ).

The relevant information (cenobamate is very persistent (vP) in aquatic systems) is correctly reflected in the Product Information.

2.3.7. Conclusion on the non-clinical aspects

The application is considered approvable from a non-clinical point of view.

However, the applicant should submit the following post-authorisation non-clinical studies:

- the embryo-foetal development study of cenobamate in rat.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 7: Tabular overview of the cenobamate clinical studies

Study number	Objective	Study design	Subjects
Phase III, epilepsy			
YKP3089C021	PK, S	OL, uncontrolled	1347
Phase II, epilepsy			
YKP3089C013	Dose finding, E, S	Randomised, DB, PBO-controlled; included OL extension	222
YKP3089C017	Dose finding, E, S	Randomised, DB, PBO-controlled; included OL extension	437
Phase II, photosensitive epilepsy			
AA40616	Proof of concept	Non-randomised, uncontrolled, single-dose	7
Phase I, healthy volunteers			
AA39450	PK (food effect); S	OL, randomised, single-dose, 2-way crossover, 2-sequence	16
YKP3089C019	PK (BE); S	OL, randomised, single-dose, 2-period, 2-sequence crossover	14
YKP3089C032	PK (rel. BA; food effect); S	OL, randomised, single-dose, crossover	60
AA22780	S, PK	Randomised, DB, PBO-controlled, SAD	110
AA24143	S, PK	Randomised, DB, PBO-controlled, MAD	50
YKP3089C009	S, PK	Randomised, DB, PBO-controlled, MAD	20
YKP3089C018	S, PK	Randomised, DB, PBO-controlled, MAD	30
AA41857	ADME, S	OL, single-dose, mass balance, single dose	6
YKP3089C030	PK, S (elderly subjects)	Uncontrolled, OL, single-arm, single-dose	26
YKP3089C006	DDI (Ortho-Novum®)	OL, multiple-dose, 1-sequence, 3-period	28
YKP3089C010	DDI (Divalproex)	OL, multiple-dose, 1-sequence, 3-period	16
YKP3089C011	DDI (carbamazepine)	OL, multiple-dose, 1-sequence, 3-period	16
YKP3089C014	DDI (carbamazepine)	OL, multiple-dose, 1-sequence, 2-period	16
YKP3089C016	DDI (phenytoin)	OL, multiple-dose, 1-sequence, 4-period	16
YKP3089C022	DDI (phenobarbital)	OL, single-arm, 2-treatment	16
YKP3089C026	DDI (P450 probe drugs[1])	OL, within-group comparison, 1 fixed treatment	24
YKP3089C029	Alcohol interaction study	DB, randomised, single-dose, 4-way crossover	32
YKP3089C020	Thorough QT study	Randomised, DB, PBO/active-controlled, parallel study, nested crossover design	108
YKP3089C031	PK, S (Japanese subjects)	Randomised, DB, PBO-controlled, single ascending dose	32
Phase I, volunteers with renal or hepatic impairment			
YKP3089C027	PK, S (hepatic impairment)	OL, uncontrolled, parallel-group, single-dose	24
YKP3089C028	PK, S (renal impairment)	OL, uncontrolled, parallel-group, single-dose	31
Phase I, healthy volunteer non-dependent, recreational drug users with sedative experience			

Study number	Objective	Study design	Subjects
YKP3089C024	Human abuse potential study	Single-dose, randomised, DB, PBO/active-controlled, double-dummy, 10-sequence, 5-way crossover	53

2.4.2. Pharmacokinetics

The PK characteristics of cenobamate were determined based on studies using human biomaterials, 26 clinical studies with PK data, and 2 population PK analyses.

Analytical methods

Plasma concentrations of cenobamate were determined using validated bioanalytical methods developed according to the "FDA Guidance for Industry - Bioanalytical Method Validation, 2001" and EMA's "Guideline on bioanalytical method validation, 2012" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) for methods conducted after release of this guidance in 2012.

The determination of other drugs used in dedicated drug-drug interactions with ASMs (phenytoin, phenobarbital, carbamazepine, valproic acid), oral contraceptives (ethinyl estradiol, norethindrone), CYP450 probes (bupropion, warfarin, omeprazole, and midazolam), and special studies (alcohol, alprazolam) was performed by different bioanalytical laboratories using validated methods.

Single Ascending Oral Dose Study in Healthy Volunteers (Study AA22780)

Objectives: to assess the safety and pharmacokinetics of cenobamate after single oral doses ranging from 5 to 750 mg in healthy male subjects.

Figure 2

Figure 2: Mean Plasma Concentrations of Cenobamate (Semi-log Scale) (Study AA22780)

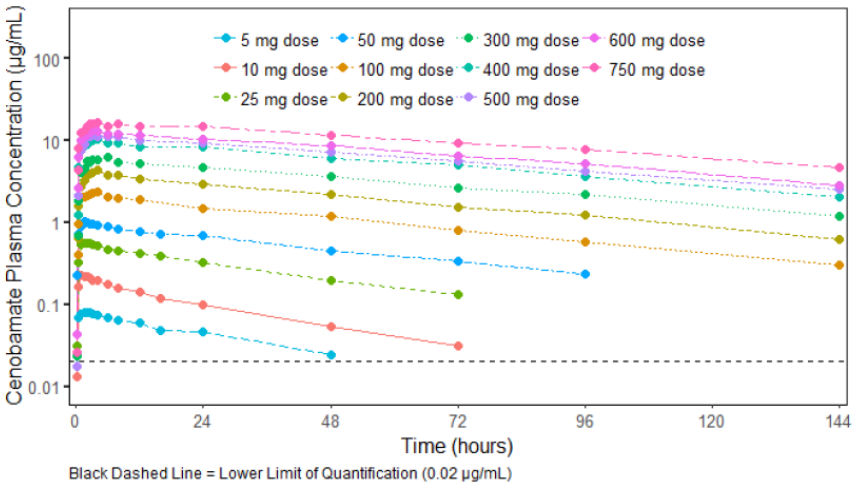


Figure 3

Table 5: Geometric Mean (%CV) Pharmacokinetic Results of Cenobamate in Plasma (Study AA22780)

Parameter	Dose group										
	5 mg (n=6)	10 mg (n=7)	25 mg (n=7)	50 mg (n=6)	100 mg (n=7)	200 mg (n=7)	300 mg (n=7)	400 mg (n=7)	500 mg (n=7)	600 mg (n=7)	750 mg (n=7)
C_{max} (µg/mL)	0.101 (16.6)	0.233 (10.2)	0.585 (11.6)	1.20 (7.91)	2.39 (18.4)	4.39 (13.1)	6.38 (6.53)	10.3 (20.6)	11.9 (12.2)	13.3 (17.8)	17.0 (12.8)
T_{max} (h) [a]	0.75 (0.50, 2.00)	1.00 (1.00, 2.00)	2.00 (0.50, 3.00)	1.75 (1.50, 4.00)	4.00 (1.00, 4.00)	3.00 (2.50, 4.00)	6.00 (2.00, 6.00)	4.00 (2.50, 6.00)	3.00 (2.12, 8.00)	3.00 (3.00, 12.00)	4.00 (2.50, 24.00)
AUC_{0-t} (µg*h/mL)	2.83 (39.0)	5.84 (38.8)	19.9 (22.8)	55.7 (21.5)	138 (12.1)	263 (16.1)	436 (10.9)	750 (21.2)	865 (13.2)	1005 (15.1)	1419 (18.8)
AUC_{inf} (µg*h/mL)	4.26 (41.7)	7.61 (45.0)	27.2 (41.0)	74.1 (29.6)	161 (17.1)[b]	313 (25.7)	539 (15.9)	925 (27.4)	1098 (20.8)	1256 (16.3)	1928 (20.7)
$t_{½}$ (h)[c]	35.9 (16.8)	30.0 (13.7)	38.1 (17.2)	47.9 (8.93)	50.2 (15.0)[b]	54.7 (16.1)	60.4 (11.2)	59.8 (12.2)	64.1 (13.9)	61.0 (10.1)	75.6 (12.3)
CL/F (L/h)[c]	1.26 (0.551)	1.42 (0.595)	0.986 (0.418)	0.698 (0.199)	0.629 (0.111)[b]	0.656 (0.158)	0.562 (0.0880)	0.446 (0.125)	0.463 (0.0900)	0.483 (0.0826)	0.396 (0.0855)
V_d/F (L)[c]	55.4 (8.07)	51.9 (4.41)	47.0 (6.59)	46.3 (6.04)	44.1 (8.86)[b]	48.8 (5.05)	48.0 (5.11)	37.1 (6.19)	41.5 (3.85)	42.1 (7.39)	42.8 (8.94)

AUC_{0-t}=area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; CL/F=oral clearance; C_{max}=maximum concentration; CSR=clinical study report; CV=coefficient of variation; SD=standard deviation; $t_{½}$=apparent terminal half-life; t_{max}=time of maximum concentration; V_d/F=apparent volume of distribution.

Median (minimum, maximum)

[b] n=6, due to insufficient samples in the terminal phase to calculate half-life and half-life dependent parameters for 1 subject.

[c] Arithmetic mean (±SD)

Conclusions:

• Cmax increased in a dose-proportional manner after single doses from 5 to 750 mg.

• AUC increased more than proportionally with single doses from 5 to 750 mg.

• Multiple peaks in the individual concentration vs time curves suggest that cenobamate undergoes entero-hepatic recirculation.

Single Ascending Oral Dose Study in Healthy Japanese Volunteers (50 mg, 100 mg, 200 mg, 400 mg) (Study YKP3089C031)

Objectives: to assess the safety and pharmacokinetics of cenobamate after single oral doses ranging from 50 to 400 mg in healthy Japanese male subjects.

Figure 4

Figure 3: Mean Plasma Concentrations of Cenobamate (Linear Scale with Semi-log Scale Inset) (Study YKP3089C031)

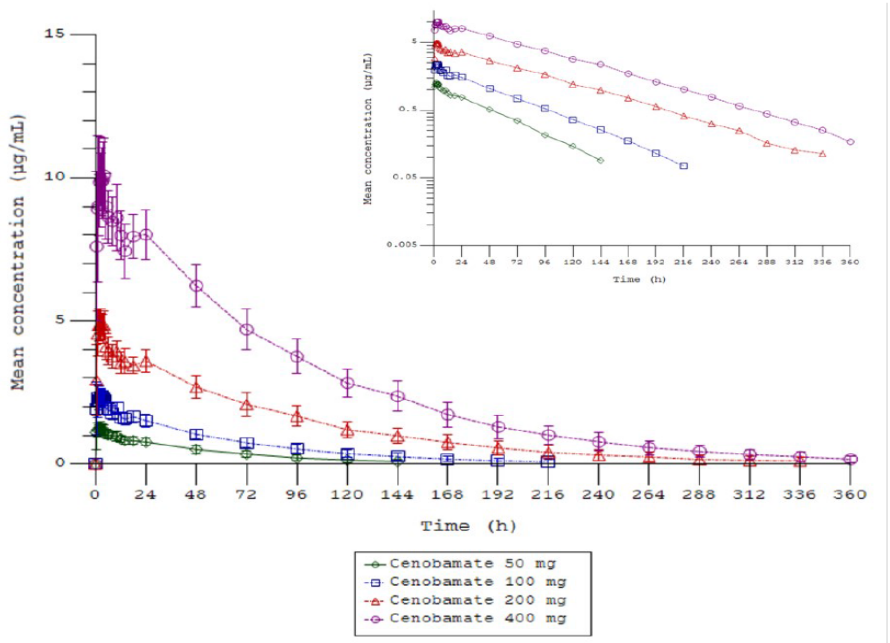


Figure 5

Table 6: Geometric Mean (Geo %CV) Pharmacokinetic Results of Cenobamate in Plasma (Study YKP3089C031)

Parameter	Dose group			
	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)
C_{max} (µg/mL)	1.46 (20.5)	2.48 (11.6)	5.22 (6.39)	10.5 (13.0)
T_{max} (h)[a]	0.75 (0.50 – 2.00)	2.00 (1.00 - 3.00)	1.75 (1.00 – 3.50)	2.25 (1.00 – 3.50)
AUC_{0-t} (µg*h/mL)	62.2 (32.0)	137 (21.5)	397 (21.4)	914 (15.8)

Conclusions:

• Cenobamate Cmax increased proportionally with dose after single doses of 50 to 400 mg.

• AUC increased more than proportionally with increasing single doses between 50 and 400 mg.

Mass Balance Study With 14C-Labeled Cenobamate (Study AA41857)

Objectives: to assess the mass balance of cenobamate following a single oral dose of 14C-labeled cenobamate and to determine the PK parameters from total radioactivity and cenobamate concentrations in plasma, to examine cenobamate erythrocyte/plasma partitioning, and to collect plasma, urine, and faeces for metabolite profiling.

Figure 6

Figure 4: Mean Total Radio activity Concentration Equivalents in Plasma and Whole Blood Total Radioactivity Versus Time (Log Scale) Following a Single Oral Dose of 50 µCi/400 mg (4x [^{14}C]-Cenobamate 12.5 µCi/100 mg Capsules) (Study AA41857)

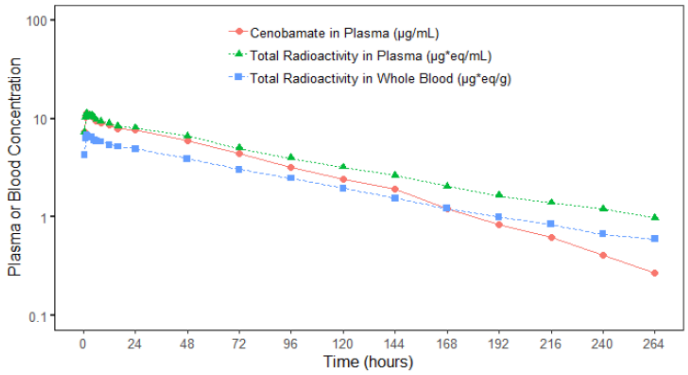


Figure 7

Table 7: Summary of Mean (%CV) Pharmacokinetic Parameters in Plasma and Whole Blood for Total Radioactivity and in Plasma for Unchanged Cenobamate Following a Single Oral Dose of 50 µCi/400 mg (4x [^{14}C]-Cenobamate 12.5 µCi/100 mg Capsules) (Study AA41857)

Parameter (N=6)	Total Radioactivity			Unchanged Cenobamate Plasma
	Whole Blood	Plasma	Blood/Plasma Ratio	
C_{max} (µg-equivalents/mL or µg/mL)[a]	7.01 (10.9)	11.6 (11.4)	0.604 (5.22)	11.9 (11.6)
AUC_{0-t} (µg-equivalents*h/mL or µg*h/mL)[b]	621 (17)	1034 (19)	NC	814 (25)
AUC_{inf} (µg-equivalents*h/mL or µg*h/mL)[b]	685 (20)	1141 (21)	0.601 (4.11)	829 (28)
T_{max} (h)[c]	1.50 (0.500, 4.00)	1.50 (0.500, 4.00)	NC	1.25 (0.500, 4.00)
$t_{½}$ (h)	81.7 (13.4)	84.6 (12.6)	NC	38.7 (52.0)

AUC_{0-t}=area under the concentration-time curve from time 0 to time of the last quantifiable concentration; AUC_{inf}=area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}=maximum concentration; CV=coefficient of variation; $t_{½}$=apparent terminal half-life; t_{max}=time of maximum concentration; N=number of subjects; NC=not calculated.

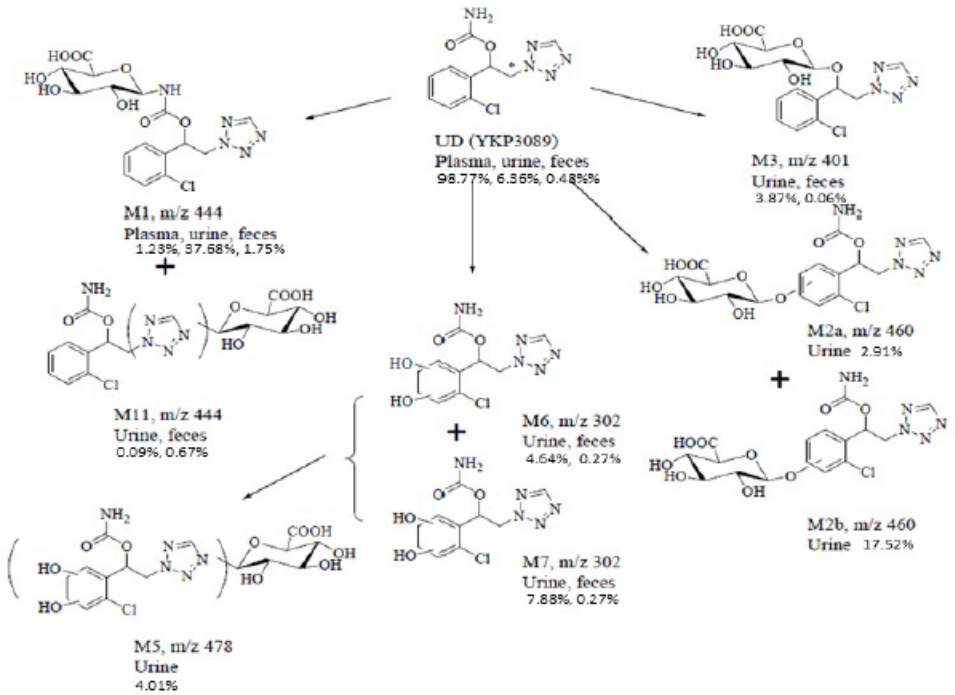
[a] Units are µg-equivalents/mL for total radioactivity or µg/mL for unchanged cenobamate

[b] Units are µg-equivalents*h/mL for total radioactivity or µg*h/mL for unchanged cenobamate

[c] Median (minimum, maximum)

Figure 8

Figure 1: Metabolites in Plasma, Urine, and Feces from Study AA41857 (Study SK08021)



M1=N-glucuronide; M2a=O-glucuronide; M2b=O-glucuronide (regio-isomer); M3=Side chain O-glucuronide; M5=Glucuronide of dihydrodiol; M6=Dihydrodiol diastereomer; M7=Dihydrodiol diastereomer; M11=N-glucuronide-tetrazole; *location of 14C radiolabel; UD=unchanged cenobamate.

Conclusions:

• The majority of a single 400 mg dose of [14C]-cenobamate reached the plasma unchanged, with little evidence of pre-systemic metabolism, suggesting high bioavailability.

• 88% of the administered dose was recovered in urine, indicating cenobamate has high permeability.

• Only ~6% of the administered dose recovered in the urine was unchanged drug, indicating cenobamate is extensively metabolised, with the metabolites being excreted in the urine.

• Blood:plasma total radioactivity ratio (0.6) and mean erythrocyte transfer ratios and erythrocyte/plasma partition coefficients (<0.15), indicate cenobamate and its metabolites did not exhibit any relevant binding to red blood cells.

Multiple Ascending Oral Dose Study in Healthy Volunteers (50 mg, 100 mg, 150 mg, and 200 mg Once Daily) (Study AA24143)

Objectives: To assess the safety, tolerability, and PK of cenobamate following multiple ascending doses of cenobamate from 50 mg to 200 mg in healthy male and female subjects.

Figure 9

Figure 5: Mean Cenobamate Plasma Concentrations Following Oral Administration of 50 mg, 100 mg, 150 mg, and 200 mg Once Daily on Day 1 (Top) and Day 14 (Bottom) (Semi-log Scales) (Study AA24143)

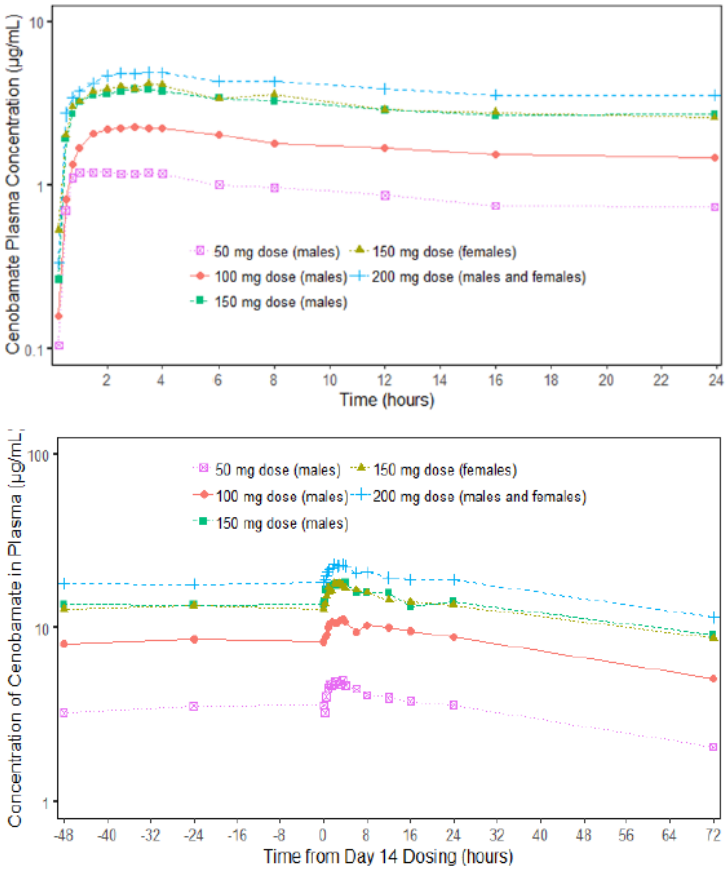


Figure 10

Table 8: Geometric Mean (%CV) Pharmacokinetic Results Following Oral Administration of 50 mg, 100 mg, 150 mg, and 200 mg Once Daily on Day 1 (Study AA24143)

Parameter	50 mg Males (N=7)	100 mg Males (N=7)	150 mg Males (N=7)	150 mg Females (N=7)	200 mg Males/Females (N=7)
C_{max} (µg/mL)	1.26 (12.2)	2.34 (8.44)	3.89 (17.5)	4.40 (10.9)	5.02 (9.05)
T_{max} (h)[a]	1.00 (0.75, 3.50)	3.00 (1.50, 4.00)	3.00 (1.00, 3.50)	2.50 (0.75, 8.00)	3.50 (2.50, 6.06)
AUC_{0-24} (µg*h/mL)	21.0 (14.0)	40.3 (13.5)	70.3 (19.2)	73.0 (15.0)	93.1 (8.09)

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours post-dose; C_{max}=maximum concentration; CSR=clinical study report; CV=coefficient of variation; t_{max}=time of maximum concentration.
[a] Median (minimum, maximum).

Figure 11

Table 9: Geometric Mean (%CV) Pharmacokinetic Results Following Oral Administration of 50 mg, 100 mg, 150 mg, and 200 mg Once Daily on Day 14 (Study AA24143)

Parameter	50 mg/day Males (N=7)	100 mg/day Males (N=7)	150 mg/day Males (N=7)	150 mg/day Females (N=7)	200 mg/day Males/Females (N=6)
C_{max} (µg/mL)	5.07 (11.0)	11.3 (9.25)	18.4 (10.7)	18.7 (19.1)	23.9 (11.6)
C_{min} (µg/mL)[a]	3.60 (14.2)	8.92 (12.1)	14.2 (9.3)	13.6 (20.9)	19.1 (11.8)
T_{max} (h)[b]	2.50 (1.00, 3.50)	3.50 (1.50, 3.50)	3.00 (1.00, 4.00)	2.06 (2.00, 3.50)	3.00 (2.00, 4.00)
$AUC_{0-\tau}$ (µg*h/mL)	96.7 (12.2)	235 (9.69)	367 (9.99)	357 (19.5)	482 (9.21)
Accumulation index[a]	4.62 (10.3)	5.85 (8.7)	5.24 (11.4)	4.91 (9.1)	5.17 (3.4)

$AUC_{0-\tau}$=area under the concentration-time curve over the dosing interval, τ (τ =24 hours); C_{max}=maximum concentration; C_{min}=minimum concentration; CV=coefficient of variation; t_{max}=time of maximum concentration.
[a] Arithmetic mean (%CV)
[b] Median (minimum, maximum)

Conclusions:

• Cmax and AUC increased more than proportionally with doses between 50 and 200 mg/day.

• Steady-state was attained approximately by Day 13, and cenobamate accumulated approximately 5-fold for all dose groups.

• Cenobamate PK was comparable in both sexes.

Multiple Ascending Oral Dose Study in Healthy Volunteers (250 mg and 300 mg Once Daily) (Study YKP3089C009)

Objectives: To assess the safety, tolerability and PK of cenobamate following multiple ascending doses of cenobamate 250 mg and 300 mg in healthy male and female subjects.

Figure 12

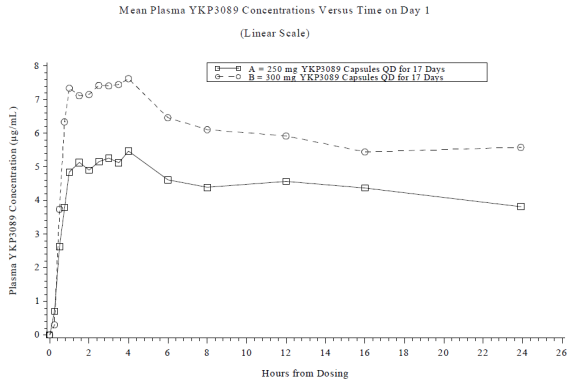


Figure 13

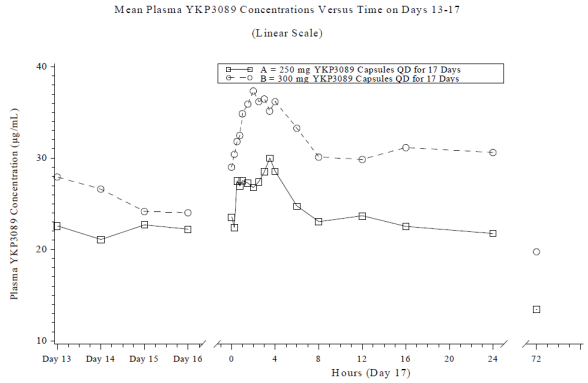


Figure 14

Table 10: Summary of Geometric Mean (%CV) Cenobamate Pharmacokinetic Parameters Following 250 mg and 300 mg Doses of Cenobamate - Single Dose (Study YKP3089C009)

Parameter	Cenobamate (Day 1)	
	250 mg (N=7)	300 mg (N=7)
C_{max} (µg/mL)	6.00 (12.1)	8.35 (17.9)
T_{max} (h)[a]	3.01 (1.00, 12.00)	3.50 (1.06, 4.00)
AUC_{0-24} (µg*h/mL)	104 (12.4)	142 (12.4)

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours post-dose; C_{max}=maximum concentration; CV=coefficient of variation; t_{max}=time of maximum concentration.
[a] Median (minimum, maximum).

Figure 15

Table 11: Summary of Geometric Mean (%CV) Cenobamate Pharmacokinetic Parameters Following 250 mg and 300 mg Doses of Cenobamate - Multiple Dose (Study YKP3089C009)

Parameter	Cenobamate (Day 17)	
	250 mg/day (N=7)	300 mg/day (N=5)
C_{max} (µg/mL)	30.6 (25.4)	38.4 (13.9)
C_{min} (µg/mL)[a]	21.8 (35.7)	30.6 (10.5)
T_{max} (h)[b]	3.50 (0.50, 4.01)	2.00 (1.01, 3.50)
$AUC_{0-\tau}$ (µg*h/mL)	552 (31.0)	757 (13.0)
Accumulation index[a]	5.43 (24.4)	5.40 (9.17)
C_{avg} (µg/mL)[a]	23.9 (29.9)	31.8 (13.2)

$AUC_{0-\tau}$=area under the concentration-time curve during the dosing interval τ (τ=24 hours); C_{avg}=average concentration at steady state; C_{max}=maximum concentration; C_{min}=minimum concentration; CV=coefficient of variation; t_{max}=time of maximum concentration.

[a] Arithmetic mean (%CV)

[b] Median (minimum, maximum)

Conclusions:

• Cmax and AUC increased fairly proportionally with increasing doses from 250 mg/day and 300 mg/day.

• Steady state was attained approximately by Day 13 and drug accumulation was approximately 5-fold.

Multiple Ascending Oral Dose Study in Healthy Volunteers Using a Titration Regimen (400 mg, 500 mg, and 600 mg Once Daily) (Study YKP3089C018)

Objectives: To assess the safety, tolerability and PK of cenobamate following multiple ascending doses of cenobamate 400 mg to 600 mg in healthy male and female subjects.

Figure 16

Figure 2 Mean Plasma YKP3089 Concentrations by Treatment Versus Time Following 400 mg (N = 7) and 500 mg (N = 5) QD Doses (Semi-Log Scale)

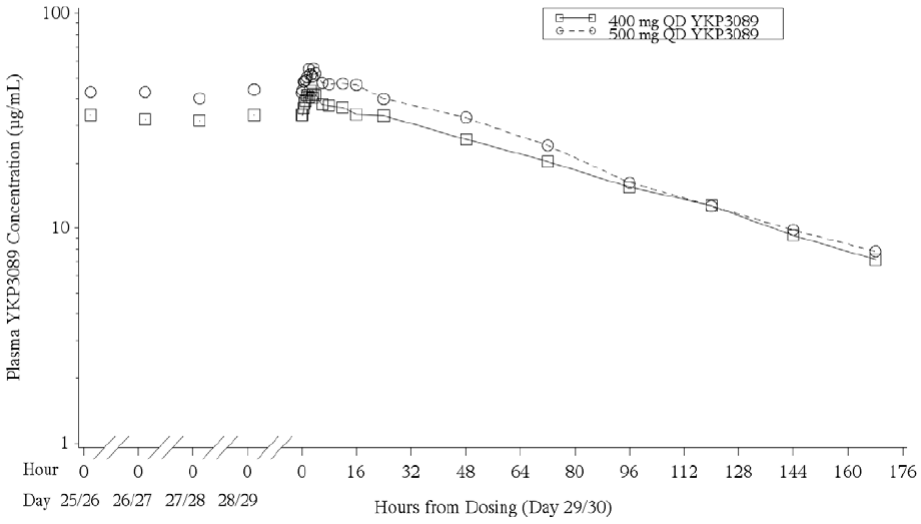


Figure 17

Table 13: Summary of Geometric Mean (%CV) Plasma Cenobamate Pharmacokinetic Parameters Following Administration of Multiple 400 mg to 500 mg QD Cenobamate Doses (Study YKP3089C018)

Parameter	Cenobamate (Day 15)[a]	
	400 mg/day (N=7)	500 mg/day (N=5)
C_{max} (µg/mL)	45.5 (17.5)	59.2 (8.34)
T_{max} (h)[b]	2.50 (0.750, 4.00)	3.50 (2.02, 16.0)
$AUC_{0-\tau}$ (µg*h/mL)	861 (17.3)	1113 (13.3)
C_{min} (µg/mL)[c]	33.4 (22.4)	40.1 (14.4)

$AUC_{0-\tau}$=area under the plasma concentration-time curve over the dosing interval, τ (τ=24 hours); C_{max}=maximum concentration; C_{min}=minimum concentration over the dosing interval; CV=coefficient of variation; QD=once daily; T_{max}=time of the maximum concentration.

[a] 400 mg/day and 500 mg/day dose data are from Day 29 and Day 30 including titration days, respectively, which is Day 15 of the targeted dose

[b] Median (minimum, maximum)

[c] Arithmetic mean (%CV)

Conclusions:

• Both Cmax and AUCtau increased proportionally with increasing doses between 400 and 500 mg/day.

• Steady state was attained approximately by Day 11 after administration of 400 and 500 mg/day.

Relative Bioavailability of 50 mg and 200 mg Tablet Strengths versus 100 mg Tablet Strength (Study YKP3089C032)

Objectives: To assess the relative bioavailability of 2×50 mg tablets compared to 1×100 mg tablet and to assess the relative bioavailability of 2×100 mg tablets compared to 1×200 mg tablet under fasted conditions, to assess the effect of food on the bioavailability of the 200 mg tablet, to assess intrasubject variability of the 200 mg strength dose under fasted conditions.

Conclusions:

• Two 100 mg cenobamate tablets are bioequivalent to one 200 mg tablet for both rate (Cmax) and extent (AUC) of absorption of cenobamate.

• Two cenobamate 50 mg tablets are bioequivalent to one cenobamate 100 mg tablet for both rate (Cmax) and extent (AUC) of absorption of cenobamate.

• There is no effect of food (as a high-fat high-calorie breakfast) on the relative bioavailability of cenobamate 200 mg tablets.

• Intrasubject variability and intersubject variability for cenobamate are relatively low for the highest oral tablet strength formulation (200 mg).

Food Effect Using Capsule Formulation (Study AA39450)

The study showed that there is no effect of food (as a high-fat high-calorie breakfast) on the relative bioavailability of cenobamate 3×100 mg capsules.

Effect of Age (Study YKP3089C030)

Objectives: To assess the PK, safety and tolerability of cenobamate in healthy elderly subjects compared to healthy young adult subjects.

Figure 18

Table 14: Treatment Comparison of Cenobamate After a Single Administration of 200 mg Cenobamate in Healthy Young and Elderly Subjects (Study YKP3089C030)

Parameter (Units)	Young Subjects (n=12) Reference[a]	Elderly Subjects (n=12) Test[a]	Test/Reference[b]
C_{max} (µg/mL)	5.4660 (4.9764; 6.0038)	5.2259 (4.7578; 5.7401)	0.95608 (0.83725; 1.0918)
$AUC_{0\text{-}last}$ (µg*h/mL)	402.72 (343.80; 471.73)	432.44 (369.18; 506.55)	1.0738 (0.85857; 1.3430)
$AUC_{0\text{-}inf}$ (µg*h/mL)	415.69 (354.81; 487.02)	440.53 (376.01; 516.11)	1.0597 (0.84710; 1.3257)

ANOVA=analysis of variance; $AUC_{0\text{-}inf}$=area under the plasma concentration-time curve from time of dosing extrapolated to infinity; $AUC_{0\text{-}last}$=area under the plasma concentration-time curve from time to the time of the last quantifiable concentration; C_{max}=maximum concentration; CI=confidence interval; LSM=least squares mean.
Note: An ANOVA on log-transformed data was used, including age group as fixed effects
[a] Geometric LSM (90% CI)
[b] Point estimate (90% CI) for the Test/Reference geometric is mean ratio derived from ANOVA

Conclusions:

• No effect of age on cenobamate Cmax was observed, and the slight increase in AUC in elderly subjects was not considered clinically meaningful.

Effect of Renal Impairment (Study YKP3089C028)

Objectives: To investigate the effect of renal impairment on the PK and the safety and tolerability of cenobamate in subjects with varying degrees of renal impairment.

Figure 19

Table 16: Treatment Comparison of Cenobamate After a Single Administration of Cenobamate in Normal Subjects or Subjects with Renal Impairment, Revised Analysis (ARV001-C028)

Renal Function	PK parameter	Geometric LSM		Geometric Mean Ratio	90% CI
		Test	Reference		
Mild v Normal (8/6)	C_{max} (µg/mL)	4.93	5.20	0.947	0.7966, 1.1258
	AUC_{last} (h*µg/mL)	429.84	306.11	1.4042	1.0746, 1.8348
	AUC_{inf} (h*µg/mL)	445.62	313.03	1.4236	1.0923, 1.8554
Moderate v Normal (6/6)	C_{max} (µg/mL)	4.77	5.20	0.9173	0.7624, 1.1035
	AUC_{last} (h*µg/mL)	439.67	306.11	1.4363	1.0791, 1.9117
	AUC_{inf} (h*µg/mL)	452.76	313.03	1.4464	1.0896, 1.9199
Severe v Normal (10/6)	C_{max} (µg/mL)	4.32	5.20	0.8293	0.7029, 0.9784
	AUC_{last} (h*µg/mL)	310.57	306.11	1.0146	0.7856, 1.3102
	AUC_{inf} (h*µg/mL)	325.25	313.03	1.0391	0.8065, 1.3386

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of the last quantifiable measurement; AUC_{inf}=area under the plasma concentration–time curve from time of dosing extrapolated to infinity; C_{max}=maximum concentration; CI=confidence interval

Conclusions:

• Systemic exposures (AUC) of cenobamate were 1.4- to 1.5-fold higher in subjects with mild (GFR 60 to <90 mL/min) or moderate (30 to <60 mL/min) renal impairment relative to subjects with normal renal function after a single cenobamate 200 mg dose.

• Subjects with severely impaired renal function (GFR <30, not requiring dialysis) did not have clinically relevant differences in exposures (Cmax and AUC) after a single cenobamate 100 mg dose relative to subjects with normal renal function.

• The results from the severe RI group were unanticipated (plasma exposure apparently lower than for the normal renal function group after dose normalisation) and possibly related to a difference in PK at a lower dose of cenobamate in the severe RI group (100 mg vs. 200 mg).

Effect of Hepatic Impairment (Study YKP3089C027)

Objectives: To investigate the effect of hepatic impairment on the PK and the safety and tolerability of cenobamate in subjects with varying degrees of hepatic impairment.

Figure 20

Table 17: Treatment Comparison of Cenobamate After a Single Administration of Cenobamate in Normal Subjects or Subjects with Hepatic Impairment, (Study YKP3089C027)

Hepatic Function	PK parameter	Geometric LSM		Geometric Mean Ratio	90% CI
		Test	Reference		
Mild v Normal (8/8)	C_{max} (µg/mL)	5.6936	4.6290	1.2300	1.0383, 1.4570
	AUC_{last} (h*µg/mL)	540.87	281.80	1.9193	1.5081, 2.4427
	AUC_{inf} (h*µg/mL)	559.76	288.91	1.9375	1.5095, 2.4868
Moderate v Normal (8/8)	C_{max} (µg/mL)	4.1795	4.6290	0.9029	0.7622, 1.0696
	AUC_{last} (h*µg/mL)	599.18	281.80	2.1262	1.6706, 2.7061
	AUC_{inf} (h*µg/mL)	664.57	288.91	2.3003	1.7922, 2.9524

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of the last quantifiable measurement; AUC_{inf}=area under the plasma concentration–time curve from time of dosing extrapolated to infinity; C_{max}=maximum concentration; CI=confidence interval

Conclusions:

• Systemic exposures (AUC) of cenobamate were 1.9-fold and 2.3-fold higher in subjects with mild hepatic impairment and moderate hepatic impairment, respectively, relative to subjects with normal hepatic function after a single cenobamate 200 mg dose.

Divalproex Sodium Interaction Study in Healthy Subjects (Study YKP3089C010)

Objectives: To assess the effect of a multiple dose regimen of cenobamate on the plasma PK of divalproex in healthy subjects and to assess the effect of a multiple-dose regimen of divalproex on the plasma PK of cenobamate in healthy subjects. There were no drug interactions between cenobamate and divalproex following once daily 150 mg dose of cenobamate.

Phenytoin Interaction Study in Healthy Adult Subjects (Study YKP3089C016)

Objectives: To determine the effect of multiple doses of cenobamate on the PK of phenytoin and to determine the effect of multiple doses of phenytoin on the PK of cenobamate when given orally to healthy subjects.

Conclusions:

• Cenobamate 200 mg/day increased phenytoin exposures (Cmax +67% and AUC0-τ +84%) when co-administered with phenytoin 300 mg/day.

• Phenytoin 300 mg/day reduced cenobamate exposures (Cmax -27% and AUC0-τ -28%) when co-administered with cenobamate 200 mg/day.

Phenobarbital Interaction Study in Healthy Adult Subjects (Study YKP3089C022)

Objectives: To assess the effect of cenobamate on the PK of phenobarbital at steady state, to assess the effect of phenobarbital on the PK of cenobamate at steady state using historical data of cenobamate administered alone and to evaluate the safety and tolerability of cenobamate and phenobarbital when co-administered.

Co-administration of phenobarbital 90 mg/day with cenobamate 200 mg/day increased phenobarbital exposures (Cmax,ss +34% and AUC0-τ +37%), but reduced cenobamate AUC (-15%).

Carbamazepine Interaction Study in Healthy Adult Subjects (Study YKP3089C011)

Objectives: To determine the effect of multiple doses of cenobamate on the PK of carbamazepine and to determine the effect of multiple doses of carbamazepine on the PK of cenobamate given orally to healthy subjects.

Conclusions:

• Cenobamate 200 mg/day reduced carbamazepine exposures (Cmax -34% and AUCtau -35%). However, this result is likely an over-estimate of the effect due to insufficient time (<3 weeks) for CYP3A4 autoinduction by carbamazepine.

• Co-administration of carbamazepine 200 mg BID and cenobamate 200 mg QD does not appear to affect cenobamate exposures, but this result is limited by the lack of a washout after carbamazepine co-administration.

Carbamazepine Interaction Study in Healthy Adult Subjects (Study YKP3089C014)

Objectives: To confirm the possible effect of cenobamate on carbamazepine disposition and to assess safety and tolerability when cenobamate and carbamazepine were co-administrated.
Conclusions:

• Co-administration of cenobamate 200 mg/day with carbamazepine 200 mg BID reduced carbamazepine exposures (Cmax -23% and AUCtau -24%) and increased plasma exposures of carbamazepine epoxide (Cmax +28% and AUCtau +20%). This result is more representative of the effect of cenobamate on carbamazepine than the first study (YKP3089C011) since autoinduction of CYP3A4 (4 weeks) was accounted for in the study design.

• The decrease in carbamazepine exposure and increase in its epoxide metabolite exposure confirmed that cenobamate 200 mg/day is a weak inducer of CYP3A4.

Reciprocal Effects of Co-administered Oral Contraceptives (Study YKP3089C006)

Objectives: To assess the effect of a multiple-dose regimen of cenobamate on the PK of oral contraceptives in healthy adult female subjects, to assess the effect of a multiple-dose regimen of oral contraceptives on the PK of cenobamate, and to assess the safety and tolerability of the co-administration of cenobamate with oral contraceptives.

Conclusions:

• Co-administration of cenobamate 100 mg/day with Ortho-Novum 1/35® increased the exposure of norethindrone (AUC0-τ +37%) but did not have a clinically relevant effect on Cmax or the exposure of ethinyl estradiol.

• Co-administration of Ortho-Novum 1/35® with cenobamate had no relevant effect on the PK of cenobamate.

Effects on Co-administered P450 Substrates (Study YKP3089C026)

Objectives: To assess the influence of cenobamate on the PK of CYP probe drugs (midazolam [CYP3A], warfarin [CYP2C9], omeprazole [CYP2C19], and bupropion [CYP2B6]) as a means of predicting DDIs.

Conclusions:

• Cenobamate 200 mg/day reduced exposures of bupropion (Cmax -23% and AUClast -39%), and increased the metabolite-to-parent ratios (4-fold), indicating that cenobamate induces CYP2B6.

• Cenobamate 100 mg/day and 200 mg/day reduced exposures of midazolam (Cmax -27% and AUClast -27% at 100 mg/day; Cmax -61% and AUClast -72% at 200 mg/day), and increased the 1-hydroxymidazolam metabolite-to-parent ratios (2-fold at 100 mg/day and 5-fold at 200 mg/day), indicating cenobamate induces CYP3A4.

• Cenobamate 200 mg/day increased exposures of omeprazole (Cmax +83% and AUClast +107%), and decreased the 5-hydroxyomeprazole metabolite-to-parent ratios (4.5-fold), indicating cenobamate inhibits CYP2C19.

• Cenobamate 200 mg/day did not affect the activity of CYP2C9 isoenzyme

Reciprocal Effects of Co-administered Alcohol (Study YKP3089C029)

Objectives: To compare the pharmacodynamics effects and PK of a single dose of cenobamate, of ethanol, and of the combination of cenobamate and ethanol.

Co-administration of 200 mg cenobamate and alcohol does not alter the exposures of either cenobamate or ethanol.

Population PK Model of Cenobamate (Study SK16007)

Objectives: To describe the plasma concentration time profiles and characterise the variability in the PK of cenobamate after oral administration, to identify relevant covariates, such as age, weight, body surface area (BSA), body mass index, race/ethnicity, gender, CLcr, bilirubin, AST, ALT, alkaline phosphatase, and concomitant ASM medications (carbamazepine, clobazam, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate and valproic acid) that may potentially influence the PK of cenobamate.

The analysis includes data from 8 Phase 1 studies (included healthy (AA22780, AA24143, YKP3089C009, YKP3089C018, and YKP3089C006), elderly (YKP3089C030), renal impaired (YKP3089C028), and hepatic impaired (YKP3089C027) subjects), 2 adequate and well-controlled studies (YKP3089C013, YKP3089C017), and 1 Phase 3 open-label safety study (YKP3089C021) in epilepsy patients.

Conclusions:

• Cenobamate PK was well described by a model with first-order absorption following an absorption lag, followed by 2-compartment disposition and elimination.

• There is low to moderate inter-individual variability in CL/F, leading to less overlap in exposure between doses.

• Cenobamate exposures may be ~20% higher in underweight subjects and ~20% lower in obese subjects.

• Co-administration of clobazam with cenobamate 100, 200, or 400 mg/day is predicted to increase cenobamate exposures (AUC +24%); however, this change is not expected to be clinically relevant.

• While there were statistically significant effects of bilirubin, carbamazepine, and race on CL/F or V1/F, these effects were all small and were not clinically relevant.

• Lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and valproic acid did not significantly affect the disposition of cenobamate.

• The need to adjust the cenobamate dose based on these results would be most likely limited because cenobamate would be slowly titrated to an effective dose.

Population PK Model to Assess the Effect of Cenobamate on the PK of Concomitant ASMs (Study SK16006)

Objectives: To develop Population PK models describing how cenobamate affects exposure to other commonly used ASMs when given as adjunct therapy.

The analysis includes data from the clinical studies YKP3089C013, YKP3089C017 and YKP3089C021 in epilepsy patients.

Conclusions:

• There are no clinically relevant changes in ASM concentrations when cenobamate 100 mg/day is administered concomitantly with any of the ASMs.

• When cenobamate 200 mg/day is coadministered with ASMs, no clinically changes in ASM concentrations is predicted with the exception of a 35% reduction in lamotrigine concentrations.

• When cenobamate 400 mg/day is coadministered with ASMs, phenytoin concentrations are expected to be 60% higher, carbamazepine concentrations are expected to be ~35% lower, and lamotrigine concentrations are expected to be ~50% lower.

• Insufficient data were available to predict the effect of cenobamate on concentrations of phenobarbital, lacosamide, clobazam, perampanel, topiramate.

Absorption

As cenobamate was never administered intravenous, its oral bioavailability is unknown. However, based on the mass balance study AA41857, where 88% of the dose was collected in the urine and on the very low clearance, the bioavailability is expected to be high. Cenobamate should be considered as a BCS class 1 drug, with high permeability and high solubility. Its absorption is very fast with a Tmax around 2 to 3.5 hours post-dose. Multiple late peaks were observed suggesting enterohepatic recirculation. No major food effect was observed for cenobamate after a high-fat high-calorie meal, with bioequivalence in Cmax and AUC between fasting and fed conditions.

Distribution

Cenobamate volume of distribution in most of the studies was in the order of 40-50L. Plasma protein binding is approximately 60% and independent of the plasma concentration. Whole blood to plasma ratio of cenobamate is 0.60.

Elimination and Metabolism

The elimination half-life of cenobamate is around 50h, and is mainly eliminated by the urine as metabolites, with only a small fraction of the dose (around 7%) appearing in the urine as cenobamate. Almost no cenobamate appears in the faeces.

Cenobamate is extensively metabolised to multiple metabolites that are further metabolised and/or excreted primarily in urine. Cenobamate is metabolised by both UGT conjugation and CYP oxidation.

UGT enzymes include UGT2B7 and to a lesser extent UGT2B4, and CYP enzymes include CYP2E1, CYP2A6, CYP2B6, and to a lesser extent CYP2C19 and CYP3A4/5.

The mass balance study showed that the majority of a single 400 mg dose reached the plasma unchanged, with little evidence of pre-systemic metabolism. No major metabolites (i.e. >10% of total drug-related material) were identified in human plasma. The N-glucuronide of cenobamate (M1) was the only circulating metabolite detected in plasma and its exposure (AUC) was found to be 1.2% of the parent drug. M1 metabolite is also the main specie appearing in the excreta, with a cumulative of 39.43% of the dose until the 264h post dose. Other relevant metabolites are the O-glucuronide (M2a) with 17.52% and the dihydrodiol diastereomer (M7) with 8.15% of the dose.

Dose proportionality and time dependencies

Cenobamate PK seems to be linear across the therapeutic dose range of 100 to 400 mg/day in steady state. However systemic exposures increase in a greater than dose-proportional manner at doses less than 100-200 mg/day in single dose.

Special populations

Impaired renal function

Cenobamate exposure increases with the reduction of the renal function. This increase is in the order of 1.5 times for both mild and moderate impaired subjects. For the severe impaired subjects, results are contradictory with a similar exposure to the healthy subjects.

Impaired hepatic function

Systemic exposures (AUC) of cenobamate were 1.9-fold and 2.3-fold higher in subjects with mild hepatic impairment and moderate hepatic impairment, respectively, relative to subjects with normal hepatic function after a single cenobamate 200 mg dose.

Weight

Simulations using the population PK model showed that subjects with low weights may have ~25% higher cenobamate exposures and those with high weights may have ~20% lower exposures than those with mean weights.

Pharmacokinetic interaction studies

Effect of Concomitant ASMs on the PK of Cenobamate

Based on results from dedicated studies and population PK analyses, some antiepileptic drugs (ASMs) had an effect on cenobamate exposures.

The effects of ASMs on the PK of cenobamate from the dedicated studies showed that phenobarbital and phenytoin decreased cenobamate exposures, but neither divalproex nor carbamazepine had an effect on cenobamate exposure.

Table 8: Effect of Concomitant ASMs on PK of Cenobamate

Co-administered Drug PK Parameter	Cenobamate + ASM versus Cenobamate Alone Ratio[a]	90% CI
Phenytoin		
C_{max}	0.7306	0.6827, 0.7820
$AUC_{0-\tau}$	0.7170	0.6725, 0.7644
Phenobarbital		
C_{max}	0.9027	0.8273, 0.9850
$AUC_{0-\tau}$	0.8450	0.7739, 0.9227
Divalproex		
C_{max}	1.0000	0.9750, 1.0256
$AUC_{0-\tau}$	1.0897	1.0620, 1.1182
Carbamazepine		
C_{max}	0.9733	0.9366, 1.0115
$AUC_{0-\tau}$	0.9736	0.9479, 1.0001

ASM=antiseizure medication; ANOVA=analysis of variation; $AUC_{0-\tau}$= area under the plasma concentration-time curve over the dosing interval, τ; C_{max}=maximum concentration; LSM=least squares mean; PK=Pharmacokinetic.
[a] Geometric LSM ratio = Cenobamate + ASM (test)/Cenobamate alone (reference) - Parameters were ln-transformed prior to analysis and geometric LSMs were calculated by exponentiating the LSM from the ANOVA

The population PK study SK16007 showed that carbamazepine and clobazam both significantly affected the oral clearance of cenobamate by a 15% increase and a 19% decrease, respectively. Simulations showed that the effects of carbamazepine on cenobamate AUC were not clinically relevant given that the 90% confidence interval for the geometric mean ratio were within the 80 to 125 bounds. Clobazam increased the AUC of cenobamate by approximately 24%. The other ASMs tested were not found to affect significantly the disposition of cenobamate.

Effect of Cenobamate on PK of Concomitant ASMs

Based on results from dedicated studies and population PK analyses, cenobamate increases exposures of phenobarbital and phenytoin, reduces exposures of lamotrigine and carbamazepine, and has no relevant effect on levetiracetam, valproic acid, or oxcarbazepine.

Table 9: Effect of Cenobamate on PK of Concomitant ASMs

Drug PK Parameter	ASM + Cenobamate versus ASM Alone Ratio[a]	90% CI
Phenobarbital		
C_{max}	1.3380	1.2843, 1.3938
$AUC_{0-\tau}$	1.3745	1.3292, 1.4214
Phenytoin		
C_{max}	1.6700	1.5507, 1.7984
$AUC_{0-\tau}$	1.8417	1.6906, 2.0062
Carbamazepine (YKP3089C011)		
C_{max}	0.6634	0.6234, 0.7058
$AUC_{0-\tau}$	0.6547	0.6183, 0.6932

Drug **PK Parameter**	**ASM + Cenobamate versus ASM Alone Ratio**[a]	**90% CI**
Carbamazepine (YKP3089C014)		
C_{max}	0.7691	0.7142, 0.8283
$AUC_{0-\tau}$	0.7646	0.7118, 0.8214
Divalproex		
C_{max}	1.0477	0.9357, 1.1732
$AUC_{0-\tau}$	1.0968	0.9903, 1.2147

ASM=antiseizure medication; ANOVA=analysis of variance; $AUC_{0-\tau}$= area under the plasma concentration-time curve over the dosing interval, τ; C_{max}=maximum concentration; PK=Pharmacokinetic; LSM=least squares mean.
[a] Geometric LSM ratio = ASM+Cenobamate (test)/ASM alone (reference) - Parameters were ln-transformed prior to analysis and geometric LSMs were calculated by exponentiating the LSM from the ANOVA

The population PK Study SK16006 showed the following:

• There was no clinically relevant effect of cenobamate on valproic acid, oxcarbazepine, or levetiracetam concentrations during treatment with cenobamate over the 100 to 400 mg/day dose range,

• There is a dose-dependent decrease in carbamazepine concentrations during treatment with cenobamate over the 100 (-11%) to 400 mg/day (-34%) dose range,

• There is a dose-dependent decrease in lamotrigine concentrations during treatment with cenobamate over the 100 (-21%) to 400 mg/day (-52%) dose range,

• There is a dose-dependent increase in phenytoin concentrations during treatment with cenobamate over the 100 (+10%) to 400 mg/day (+60%) dose range,

• Insufficient data were available to estimate the effect of cenobamate on the PK of phenobarbital, lacosamide, clobazam, perampanel, or topiramate.

2.4.3. Pharmacodynamics

The PD characteristics of cenobamate were determined using exploratory pharmacodynamic endpoints in the early-phase studies to investigate the primary pharmacology and the exposure/effect. A PK-PD exposure-response Model was also developed to support the selected dosing regimen. A cardiac safety study was conducted to evaluate the risk of QT/QTc prolongation. In addition, a dedicated Proof of Principle study to evaluate the PD effect with a Photo-Induced Paroxysmal EEG-Response, together with a human abuse potential study and an alcohol interaction study, contributed to the PD profile assessment of cenobamate.

Mechanism of action

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.

Primary and Secondary pharmacology

Primary Pharmacology

Primary PD is based on clinical data from the 2 clinical phase 2 studies (C013 and C017) and a small Proof of Principle study (AA40616).

Proof of Principle study (AA40616) - Effect of Cenobamate on Photo-paroxysmal Response in Epilepsy Subjects Phase 2a, non-randomised, uncontrolled, single blind (blinded subjects in the clinical phase and blinded clinical expert for electroencephalogram (EEG) interpretation), increased single dose from 100 to 400 mg/day with 48-hour observation period, to evaluate the onset and duration of the PD effect of cenobamate.

The primary objective of the study was to explore the PD effect of cenobamate on the intermittent photic stimulation (IPS) induced photo-paroxysmal EEG response in subjects with epilepsy. The secondary objectives were to assess the temporal relationship of this antiepileptic effect with plasma concentrations of cenobamate and, to assess the tolerability of a single dose of cenobamate in subjects with epilepsy.

Figure 21

Table 37: Overall Proportion (%) of Subjects Administered Each Dose of Cenobamate Experiencing Complete Suppression, Partial Suppression, or No Change in IPS Sensitivity Versus Day -1 (Placebo) (Study AA40616)

Response	Cenobamate 100 mg	Cenobamate 250 mg	Cenobamate 400 mg
	Proportion (%)	Proportion (%)	Proportion (%)
Complete suppression[a]	0/3 (0)	1/4 (25)	1/4 (25)
Partial suppression[b]			
Eye closure	0/3 (0)	2/4 (50)	1/4 (25)
Eyes closed	1/3 (33)	3/4 (75)	1/4 (25)
Eyes opened	0/3 (0)	1/4 (25)	0/4 (0)
Most sensitive eye condition	0/3 (0)	3/4 (75)	1/4 (25)
Complete or partial suppression in the most sensitive eye condition	0/3 (0)	3/4 (75)	1/4 (25)
No change[c]	2/3 (66.7)	0/4 (0)	2/4 (50)

IPS=intermittent photic stimulation; PPR=photo-paroxysmal response; PR=photosensitivity range.
Note: Subjects are not mutually exclusive among 3 eye conditions. The most sensitive eye condition is defined as the eye condition with the largest PR on Day -1 averaged across all time points
[a] Complete suppression=PR reduced to 0 over at least 1 testing time point for all 3 eye conditions within the same day if baseline PPR at the same time point for each eye condition was larger than 0
[b] Partial suppression=PR reduced by at least 3 points over at least 3 testing times within 1 day compared to the range at the same time points on placebo day (Day -1)
[c] No change=subjects who do not have either complete or partial suppression in any eye condition
Source: Module 5.3.4.2, AA40616 CSR, Table 11, Table 13 and Table 15

The relationship between the peak (C_{max}) and extent (AUC_{0-24}, AUC_{0-t} and AUC_{0-inf}) of exposure and cenobamate effect on IPS sensitivity is presented for the 11 records (6 patients).

AUC_{0-t} values in the range of 1-200 µg*h/mL (for 100 mg dose) resulted in partial suppression of IPS sensitivity in 1 out of 3 (33%) subjects and 2 out of 3 (66.7%) subjects did not have a response in suppression of IPS sensitivity. AUC_{0-t} values in the range of 401-600 µg*h/mL resulted in complete suppression in 2 out of 2 (100%) subjects with 250 mg (n=1) and 400 mg (n=1) dose levels. AUC_{0-t}

values of 201-400 µg*h/mL resulted in partial suppression of IPS sensitivity in 4 out of 6 (67%) subjects with 250 mg (n=3) and 400 mg (n=1) dose levels.

Dose-responses studies (C013 and C017)

See clinical efficacy sections.

Secondary pharmacology

Human abuse liability study (YKP3089C024): Phase 1, Single-dose, randomised, DB, PBO/active-controlled, double-dummy, 10-sequence, 5-way crossover. Primary analysis population included 39 adult healthy volunteers non-dependent, recreational drug users with sedative experience, that completed all treatment periods and had at least 1 PD assessment (relevant scales and tests)

Objectives: To evaluate safety/abuse potential of single oral doses of cenobamate (200 and 400 mg) relative to alprazolam (sedative with a known profile of abuse) and placebo.

Both doses of cenobamate (200 and 400 mg) had similar abuse potential profile and significantly lower compared to alprazolam. Primary measure (Drug Liking E_{max} value) was similar to cenobamate 200 mg and placebo. Cenobamate 400 mg differentiate from placebo on E_{max} value but showed significantly decreased peak effects even when compared to the lowest dose of alprazolam. Both doses of cenobamate were comparable to placebo on psychomotor performance and on cognitive function. Plasma concentrations of cenobamate observed in recreational sedative users were consistent with those measured in previous cenobamate clinical studies conducted in healthy subjects.

Thorough QTc study (YKP3089C020): Phase 1, randomised, DB, PBO/active-controlled, 2-arm parallel study, multiple-dose nested crossover design for the control arm, 64 days dosing in 108 adult healthy volunteers (102 completed the study; 54 received initial 50 mg/day, increasing 50 mg/week, until 500 mg/day cenobamate).

Objectives: To evaluate the effects of therapeutic dose (200 mg/day) and supratherapeutic dose (500 mg/day) of cenobamate on the baseline-adjusted, placebo-corrected, corrected QTc interval for HR using Fridericia's corrected QT interval (QTcF).

The heart rate effect on cenobamate was small with the largest mean change from baseline heart rate (ΔHR) on cenobamate was -2.7 bpm and -2.9 bpm 1 hour after dosing on Days 35 (200 mg) and 63 (500 mg), respectively. The largest mean placebo-corrected ΔHR (ΔΔHR) on cenobamate was -3.6 bpm at 12 hours on Day 63.

The largest mean change-from-baseline QTcF (ΔQTcF) on cenobamate was seen 0.5 hours after dosing on Days 35 and 63, -12.0 and -22.5 msec, respectively. The mean ΔΔQTcF 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. Nine subjects had QTcF ≥450 ms at one or more time points after dosing.

Regarding cardiac conduction (PR and QRS), the mean change-from-baseline PR (ΔPR) was mildly positive on both placebo and cenobamate at all time points on both Days 35 and 63. The largest mean placebo-corrected ΔPR (ΔΔPR) was seen at 1 hour on both days, 4.1 msec (90% CI: 1.2 to 7.1) on Day 35 and 2.8 msec (90% CI: -0.5 to 6.1) on Day 63. No effect on the QRS was noted with all mean ΔΔQRS on cenobamate within ± 1.0 msec.

Plasma exposures to cenobamate increased proportionally with increasing dose, with Mean (SD) values of AUC_{tau} (µg*hr/mL) being 476.07 (119.649) on Day 35 (200 mg QD) and 1270.2 (235.154) on Day 63 (500 mg QD).

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In general, all analytical methods were well developed, validated and with acceptable performance.

As cenobamate was never administered intravenous, its oral bioavailability is unknown. However, based on the available data, the bioavailability is expected to be high and cenobamate should be considered as a BCS class 1 drug, with high permeability and high solubility. Its absorption is very fast with a Tmax ranging from 1 to 4 hours post-dose.

No major food effect was observed after a high-fat high-calorie meal, with bioequivalence in Cmax and AUC between fasting and fed conditions.

The volume of distribution in most of the studies was in the order of 40-50L. Plasma protein binding is approximately 60% and independent of the plasma concentration. Whole blood to plasma ratio of cenobamate is 0.60.

The elimination half-life of cenobamate is around 50h, and is mainly eliminated by the urine as metabolites, with only a small fraction of the dose (around 7%) appearing in the urine as cenobamate.

Cenobamate is extensively metabolised to multiple metabolites that are further metabolised and/or excreted primarily in urine. Cenobamate is metabolised by both UGT conjugation and CYP oxidation. UGT enzymes include UGT2B7 and to a lesser extent UGT2B4, and CYP enzymes include CYP2E1, CYP2A6, CYP2B6, and to a lesser extent CYP2C19 and CYP3A4/5.

No major metabolites (i.e. >10% of total drug-related material) were identified in human plasma. The N-glucuronide of cenobamate (M1) was the only circulating metabolite detected in plasma and its exposure (AUC) was found to be 1.2% of the parent drug.

Cenobamate PK seems to be linear across the therapeutic dose range of 100 to 400 mg/day in steady state. However, systemic exposures increase in a greater than dose-proportional manner at doses less than 100-200 mg/day in single dose. This may be due to a saturation of one of the multiple metabolic routes.

Dedicated clinical study on renal impaired subjects resulted in contradictory results, with an exposure increase of 1.5 times for mild and moderate impaired subjects but lack of effect on severe impaired subjects. This was further discussed and explained, with simulation using the population PK model, by the evaluation of the demographic differences and inter-individual variability. Based on the results, it is agreed that a maximum dose in patients with renal impairment at 300 mg/day should be recommended. Cenobamate should not be used in patients with end-stage renal disease or patients undergoing haemodialysis.

Systemic exposures of cenobamate were 1.9-fold and 2.3-fold higher in subjects with mild hepatic impairment and moderate hepatic impairment, respectively, relative to subjects with normal hepatic function after a single cenobamate 200 mg dose. The CHMP agreed that the maximum recommended dose in patients with mild and moderate hepatic impairment is 200 mg per day. Use in patients with severe hepatic impairment is not recommended.

Although statistically significant effects of race were observed in the population PK model, these were not clinically relevant, and no dose adjustment based on race/ethnicity is required. Weight has a significant effect on cenobamate exposure, and simulations showed that subjects with low weights may have ~25% higher exposures and those with high weights may have ~20% lower exposures than those with mean weights. The CHMP agreed that it may be clinically relevant. Given that cenobamate

treatment should be initiated with slow titration to recommended dose and clinical response, the CHMP agreed that no specific recommendation for patients based on weight is needed when establishing a dose. However, dose adjustments may be needed in patients who experience weight changes of ≥30% of their initial body weight.

There seems to be a small but significant effect of age on the cenobamate PK, with a slight increase in the exposure in elderly subjects when compared to younger subjects. Considering the reduction of hepatic and renal functions with age, this is expected and it is sufficiently described in the SmPC.

Based on the *in vitro* data, cenobamate is predicted to cause a number of interactions with medicinal products (see non-clinical discussion). This was further investigated in the pharmacokinetic study (YKP3089C026), which showed that cenobamate may reduce exposures of products primarily metabolised by CYP3A4 and 2B6 and may increase exposures of products primarily metabolised by CYP2C19.

In addition, several drug-drug interaction studies, as well as population PK analyses, were conducted to evaluate cenobamate interactions with other antiepileptic drugs including phenytoin, phenobarbital, clobazam, lamotrigine, carbamazepine, valproic acid, lacosamide, levetiracetam and oxcarbazepine Additional clinical studies also assessed the interactions of cenobamate with oral contraceptives, CYP substrates, alcohol, and food.

None of the effects of ASMs on cenobamate are substantive enough to require specific dose adjustment of cenobamate, particularly considering the slow titration allowing for dose adjustments based on individual response and possibility for treatment-resistant patients to achieve seizure control.

Cenobamate increases exposures of phenobarbital and phenytoin and it is agreed that concentrations of these ASMs should be monitored during the cenobamate titration.

Due to a possible accumulation of desmethyl-clobazam, the active metabolite of clobazam, related to the induction of CYP3A4 (formation) and the inhibition of CYP2C19 (elimination), a dose decrease of clobazam may be required when co-administered with cenobamate.

Cenobamate reduces exposures of lamotrigine and carbamazepine. In addition, based on additional analyses on the double-blind studies data, depending on the individual response, higher dose of cenobamate may be required for efficacy when co-administered with lamotrigine. (see clinical discussion).

Cenobamate has no relevant effect on lacosamide, levetiracetam, valproic acid, or oxcarbazepine.

The relevant information regarding cenobamate interactions with other antiepileptics is correctly reflected in section 4.5 of the SmPC.

Regarding cenobamate DDI as perpetrator with CYP450 substrates, cenobamate induces the activity of CYP2B6 and CYP3A4 and inhibits the activity of CYP2C19. Cenobamate (200 mg/day) reduced plasma concentrations of substrates metabolised by CYP2B6 (-23% Cmax and -39% AUC) or CYP3A4 (-61% Cmax and -72% AUC) and increased plasma concentrations of substrates metabolised by CYP2C19 (+107% Cmax and +83% AUC). Considering the potential reduced efficacy of medicines metabolised by CYP2B6 or CYP3A4, doses of these medicines may need to be increased when used concomitantly with cenobamate. Regarding medicines metabolised by CYP2C19, in view of the potential increase in adverse reactions, doses may need to be reduced when used concomitantly with cenobamate.

Regarding cenobamate DDI as perpetrator with UGT substrates, cenobamate does not appear to increase bilirubin (substrate of UGT1A1). Also, co-administration of cenobamate with carbamazepine or lamotrigine (metabolised by UGT2B7) does not increase exposures of either ASM. Clinical data

therefore suggest that cenobamate inhibition of UGT1A1 and UGT2B7 does not have a clinically relevant effect.

Regarding DDI effects on transporters, clinical bilirubin levels (a surrogate probe for OATP1B1-mediated DDIs) suggest that OATP1B1 inhibition does not have a significant impact. An analysis of the adverse events data for patients taken cenobamate and metformim (MATE1 and MATE2K substrate) showed that there were no clinically relevant changes. *In vitro* data have shown that cenobamate inhibits OAT3, a transporter predominantly involved in the elimination of several medicinal products, and concomitant administration may therefore result in higher exposures of these medicinal products.

Interaction with oral contraceptives was investigated in a dedicated DDI study and a CYP interaction study. Data from the CYP interaction study showed that the cenobamate exert a dose-dependent induction of CYP3A4 with an anticipated reduction of estradiol exposure and risk of decreased efficacy of oral contraceptives. Based on this data, it is recommended that women of reproductive potential concomitantly using oral contraceptives should use an additional or alternative non-hormonal birth control.

Pharmacodynamics

The primary PD of cenobamate is based on the clinical data from 2 clinical phase 2 studies (C013 and C017) and a small Proof of Principle study on intermittent photic stimulation (IPS) induced photo-paroxysmal EEG response.

The secondary PD is based in the clinical data from the clinical studies on abuse potential/liability and QTc interval. The abuse potential study showed there was no significant associated differences in relevant PD endpoints, revealing that both doses of cenobamate (200 and 400 mg) were liked significantly less than alprazolam by the recreational sedative users, and neither were associated with impaired effects on psychomotor performance or cognitive function.

The clinical results from the QTc study in healthy volunteers revealed a dose-dependent shortening of the QTcF interval. The mean ΔΔQTcF 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). Reductions of the QTc interval below 340 msec were not observed. The CHMP agree that information from the QT study results and the observed shortening of the QTcF interval are correctly reflected in section 5.1 and 4.4 of the SmPC (see also clinical safety discussion).

2.4.5. Conclusions on clinical pharmacology

The CHMP agrees that the available pharmacology data are acceptable.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

The dose-response was assessed through an exposure-response model built with data from the clinical studies C013 (with 200mg dose) and C017 (with 100, 200 and 400 mg doses).

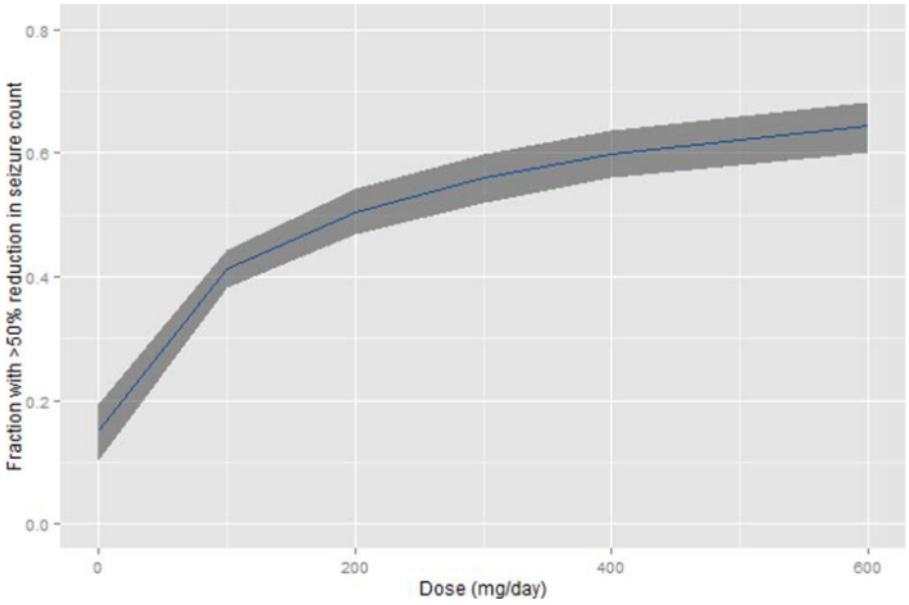
This model was used to simulate expected daily seizure count at daily doses ≤600 mg while assuming a patient population similar to that in studies C013 and C017 and a titration scheme similar to that of study C021. Data indicate that the majority of patients will show a therapeutic effect at daily doses up to 200 mg, but additional patients will likely benefit from doses up to 400 mg/day.

The simulated fraction of patients with >50% reduction in seizure frequency increased with doses up to 400 mg/day (0.42 at 100 mg/day, 0.52 at 200 mg/day, and 0.60 at 400 mg/day). Doubling the dose from 100 to 200 mg/day or 200 to 400 mg/day results in ~8-10% increase in the fraction of patients with ≥50% reduction in seizure frequency.

The simulated fraction of seizure-free patients increased with doses up to 400 mg/day (0.13 at 100 mg/day, 0.20 at 200 mg/day, and 0.28 at 400 mg/day). Doubling the dose from 100 to 200 mg/day or 200 to 400 mg/day results in a ~7-8% increase in seizure-free patients.

Figure 22

Figure 3-1: Simulated proportion of patients with >50% reduction in seizure rate during the maintenance phase; pooled data from studies C013 and C017

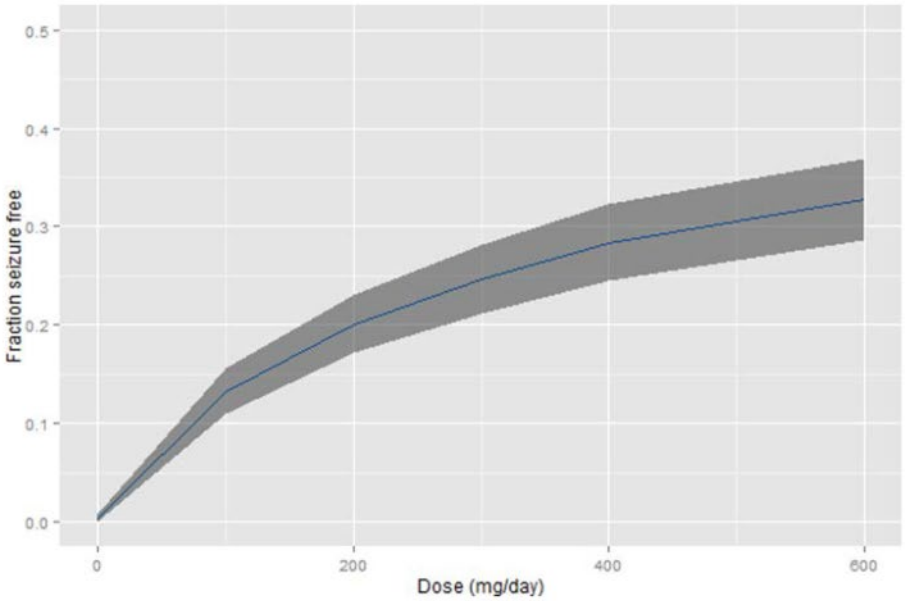


Data are shown as mean proportions with 95% confidence band

Source data: SK16008, Figure 25

Figure 23

Figure 3-2: Simulated proportion of seizure-free patients during the maintenance phase; pooled data from studies C013 and C017



Data are shown as mean proportions with 95% confidence band

Source data: SK16008, Figure 26

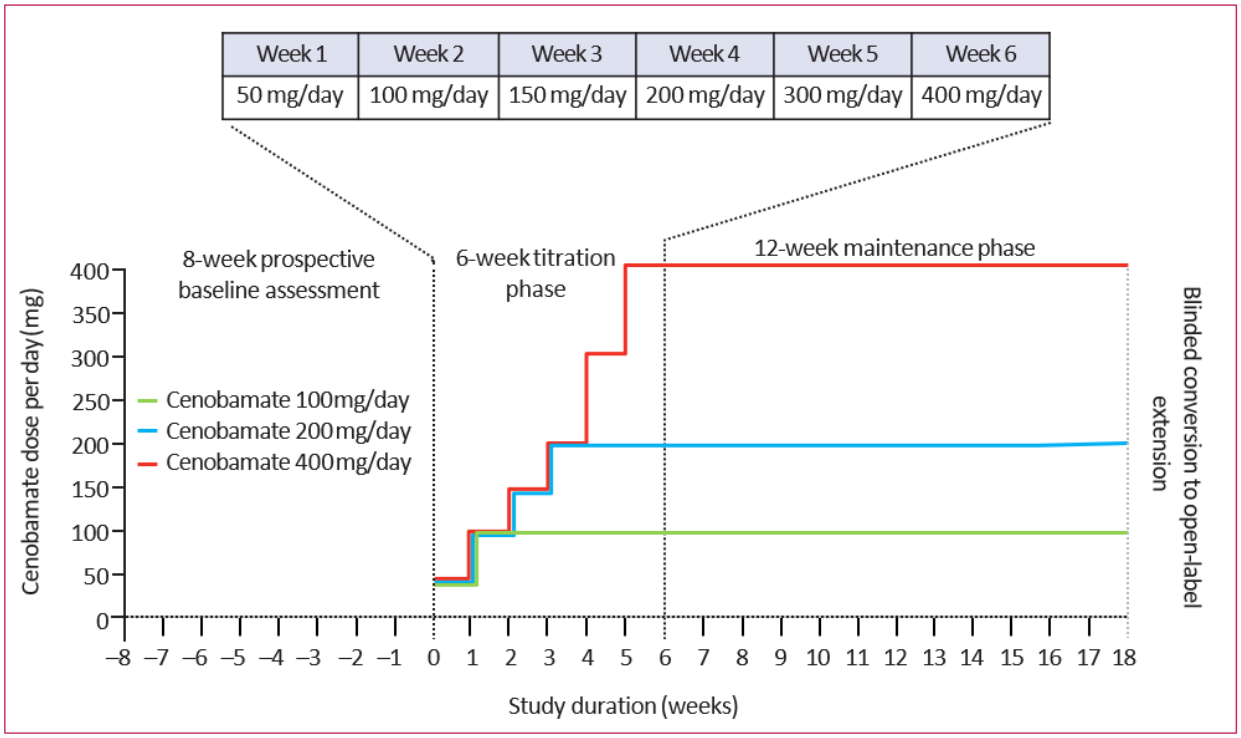
2.5.2. Main study

Study C017: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of Cenobamate as Adjunctive Therapy in Subjects with Focal Onset Seizures, with Optional Open-Label Extension

Methods

This was a double-blind, randomised, placebo-controlled study to investigate the effective dose range and safety of cenobamate as adjunctive therapy for the treatment of focal onset seizures. A total of 400 patients were planned to be randomised (1:1:1:1) to target doses of cenobamate 100, 200, or 400 mg or placebo. A sample size of 100 patients per treatment group was estimated to provide a statistical power of 80% to detect a difference of 16% in percent reduction in seizure frequency between a cenobamate dose group and placebo, at a 2-sided significance level of 0.05, assuming a standard deviation of 40% using an independent samples t test.

Figure 24: Study C017 Design



Study Participants

Inclusion criteria:

- Diagnosis of epilepsy with focal onset seizures according to ILAE criteria
- Uncontrolled focal onset seizures despite treatment with at least 1 ASM within the last 2 years
- Baseline period: ≥8 focal seizures over 8 weeks baseline with motor component, complex focal seizures, or secondarily generalised seizures; with ≥3 of these focal seizures during each of the 2 consecutive 4-week segments of the baseline period; no seizure-free interval of >25 days
- On stable doses of 1-3 ASMs for ≥4 weeks before the screening visit

Main exclusion criteria:

- Status epilepticus in the past 3 months
- Non-epileptic or psychogenic seizures; only non-motor simple focal seizures or primary generalised epilepsy; seizure clusters; Lennox-Gastaut syndrome; scheduled epilepsy surgery
- Suicidal ideation in the past 6 months or suicidal behaviour in the past 2 years (as per C-SSRS) or >1 lifetime suicide attempt
- Psychotic disorders or unstable recurrent affective disorders evident by use of antipsychotics
- Major depressive episode within the last 6 months
- Treatment with felbamate, diazepam, phenytoin, phenobarbital, or metabolites of these drugs, vigabatrin; intermittent rescue benzodiazepines >1 time/month

Patients were enrolled in the following countries: Europe: Bulgaria, Czech Republic, France, Germany, Hungary, Poland, Romania, Serbia, Spain, Ukraine, and UK Outside Europe: US; Australia; Israel; Korea; Thailand.

Treatments

Study drug refers to cenobamate or placebo. In addition to study drug, all patients were to continue their stable, concomitant ASM treatment.

Titration:

6-week titration (50 mg/day for 1 week, 100 mg/day for 1 week1, 150 mg/day for 1 week, 200 mg/day for 1 week2, 300 mg/day for 1 week, 400 mg/day for 1 week)

Patients in the 100 mg group stayed on this dose for the rest of the titration period; Patients in the 200 mg group stayed on this dose for the rest of the titration period

Dose reductions:

Week 1: no dose reduction allowed; discontinuation of patients not tolerating treatment

Week 2-6: 1 dose reduction allowed (-50 mg for patients receiving 100, 150, or 200 mg; 100 mg for patients receiving 300 or 400 mg); reduced dose given for 7-13 days; thereafter, continuation of up-titration allowed until Week 6

Continued up-titration: 1 dose reduction (50 mg) allowed before the end of Week 8

Objectives

The primary objective was to determine the effective dose range of cenobamate as adjunctive therapy for the treatment of focal onset seizures. The secondary objective was to evaluate the safety and tolerability of cenobamate in the focal epilepsy population.

Outcomes/endpoints

Primary and Secondary Efficacy Assessments:

Countries of Europe, Australia, New Zealand, and South Africa:

- The primary efficacy endpoint was the responder rate defined as a ≥50% reduction from baseline in seizure frequency (focal aware, focal unaware, focal to bilateral tonic-clonic seizures (secondarily generalised seizures)) during the maintenance phase of the double-blind treatment period.
- The secondary efficacy endpoint was the percentage change from the pre-treatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) all focal aware, focal unaware, focal to bilateral tonic-clonic seizures (secondarily generalised seizures)) compared with the maintenance phase of the double-blind treatment period.

United States and the ROW:

- The primary efficacy endpoint was the percentage change from the pre-treatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all focal aware (Type B), focal unaware (Type C), or secondarily generalised (focal to bilateral tonic-clonic) (Type D) seizures in the double-blind treatment period.

- The secondary efficacy endpoint was the responder rate defined as a ≥50% reduction from baseline in the seizure frequency during the double-blind treatment period.

Additional secondary efficacy Assessments:

- Higher response rates (≥75%, ≥90%, and 100%) of focal aware seizures, focal unaware seizures or secondarily generalised (focal to bilateral tonic-clonic) seizures seizures during the double-blind treatment period and during the maintenance compared with the baseline.
- Percentage change from baseline in seizure frequency (average monthly seizure rate per 28 days) by seizure subtypes.
- Seizure rate over time.
- Global Impression of Change (CGIC) recorded by the physician at Visit 9 or Early Termination.
- Quality of Life in Epilepsy Questionnaire (QOLIE-31-P) completed by the subject at Visit 3 and Visit 9 or Early Termination.

Pharmacokinetic Assessments:

Trough ASM concentrations (oxcarbazepine, topiramate, carbamazepine [CBZ], valproate, lamotrigine, lacosamide and levetiracetam only) during the baseline pre-treatment period were compared to those during the treatment period in subjects randomised to 100 mg/day, 200 mg/day, or 400 mg/day cenobamate or placebo to assess possible drug interactions.

Cenobamate plasma concentrations were obtained under steady-state conditions at Visits 7 and 8.

Randomisation and blinding (masking)

Randomisation was performed centrally using an IWRS. Randomisation codes were based on a block randomisation within study country. Subjects were assigned with equal chance to 1 of the 4 treatment groups based on a randomisation schedule prepared by the designated statistician.

Treatment assignments remained blinded to the subject and all study personnel until final database lock. Selected individuals from the sponsor and/or designee and at CRO could be unblinded to the study treatments on a need-to-know basis as described in CRO's standard operating procedures (SOPs) on blinding and unblinding. In the event of an emergency if unblinding was necessary, investigators could have performed emergency unblinding using the IWRS immediately, without prior contact to the study's medical monitor, if they felt it was medically necessary and that knowledge of the treatment assignment was essential for the patient's care. If such an emergency unblinding was necessary, investigators promptly documented and explained to the medical monitor or sponsor of the premature unblinding of the investigational product

Statistical methods

Hypothesis and Multiplicity

This was a superiority study.

The testing strategy for the primary efficacy endpoint was to compare each of the cenobamate dosage groups with the placebo group. Due to multiple treatment comparisons, a step-down procedure was

used to ensure the overall type I error rate is controlled at the 5% level. Each of the cenobamate dosage groups was compared with the placebo group according to the following hierarchy: 1. 200-mg dosage group versus placebo group; 2. 400-mg dosage group versus placebo group; 3. 100-mg dosage group versus placebo group

The 200-mg dosage group was compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference was detected between the 200-mg dosage group and the placebo group, the procedure would be stopped and it would be concluded that none of the cenobamate dosages are efficacious. If a statistically significant difference was detected between the 200-mg dosage group and the placebo group in favor of the 200-mg dosage group, the procedure would proceed to the next step to compare the 400-mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference was detected between the 400-mg dosage group and the placebo group in favor of the 400-mg dosage group, the procedure would proceed to the next step to compare the 100-mg dosage group with the placebo group at a 2-sided 0.05 level.

Study Populations

- Enrolled subjects: All subjects who gave informed consent to participate in the study were considered enrolled subjects.
- Intention-to-treat (ITT) subjects: All randomised subjects were considered ITT subjects.
- Modified ITT (MITT) subjects: All randomised subjects who had taken at least 1 dose of cenobamate (or placebo) and had any postbaseline seizure data were considered MITT subjects.
- MITT subjects in maintenance phase (MITT-M): All randomised subjects who had completed the titration phase and had taken at least 1 dose of cenobamate (or placebo) in the maintenance phase and had any maintenance phase seizure data were considered MITT-M subjects.
- MITT subjects who completed maintenance phase (MITT-M completer): All randomised subjects who had completed the titration phase and completed the maintenance phase were considered MITT-M completer subjects.
- Per protocol (PP) population: All randomised subjects who had no major protocol violations and had at least 80% drug compliance were considered PP subjects.
- Safety evaluable (SE) subjects: All ITT subjects were also considered SE subjects (all randomised subjects received at least 1 dose of study medication).

Primary endpoint analysis

The primary efficacy analysis of the primary endpoint in the countries of Europe, Australia, New Zealand, and South Africa was based on the MITT-M population. The testing strategy for the endpoint (responder rate) was to compare each of the cenobamate dosage groups with the placebo group. The responder rate was defined as a ≥50% reduction during the maintenance phase of the double-blind period in the seizure frequency from baseline.

Baseline phase seizure frequency was defined as the average monthly seizure rate per 28 days of all Type B, Type C, and Type D seizures. Maintenance phase seizure frequency rate was defined in a similar manner, accounting for seizures recorded during maintenance phase of the double-blind treatment period only. The data were summarised using count and percentage of subjects achieving at least a 50% response to treatment, the responder rate. The responder data were analyzed using a chi-square test.

Sensitivity analyses for the primary endpoint

Sensitivity analyses were performed for the responder rate defined as a ≥ 50% reduction during the maintenance phase of the double-blind period in the seizure frequency from baseline during the first 6 weeks of the maintenance phase, and in the last 6 weeks of the maintenance phase. An additional sensitivity analysis accounted for subjects who dropped out during the titration phase; these subjects' maintenance phase data were imputed using their available titration data.

Secondary endpoint analysis

The secondary efficacy endpoint was the percentage change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple focal motor, complex focal, or secondarily generalised seizures compared with the seizure frequency in the maintenance phase of the double-blind treatment period and was based on the MITT-M analysis population.

An ANCOVA model was fit to the ranked values of the change in seizure frequency during the maintenance phase. The ANCOVA included terms for ranked baseline seizure rate and randomised treatment group. Ties were handled using the default option in SAS. The efficacy analysis used a nonparametric approach. Because of this, effect sizes were not estimated and tested directly, as testing was made on the rank of the change in seizure frequency. However, summary tables for the actual (not the ranked) changes in seizure frequency were presented.

Sensitivity analyses for the secondary efficacy endpoint

Percentage change from the pretreatment baseline phase in seizure frequency: a) compared with the first 6 weeks of the maintenance phase of the double blind period; b) compared with the last 6 weeks of the maintenance phase of the double blind period; c) compared with the seizure frequency in the maintenance phase of the double blind period; for subjects who discontinued during titration phase of the double-blind period their titration phase seizure rate will be used in the analysis.

Pharmacokinetic Analyses:

Descriptive statistics were performed on the plasma concentrations of the concomitant ASMs obtained during steady-state concomitant treatment (Visits 7 and 8) and those at baseline (Visit 3) to assess the effect of cenobamate on these ASMs. Descriptive statistics were performed on the plasma concentrations of the cenobamate obtained during steady-state treatment (Visits 7 and 8).

Handling of missing data

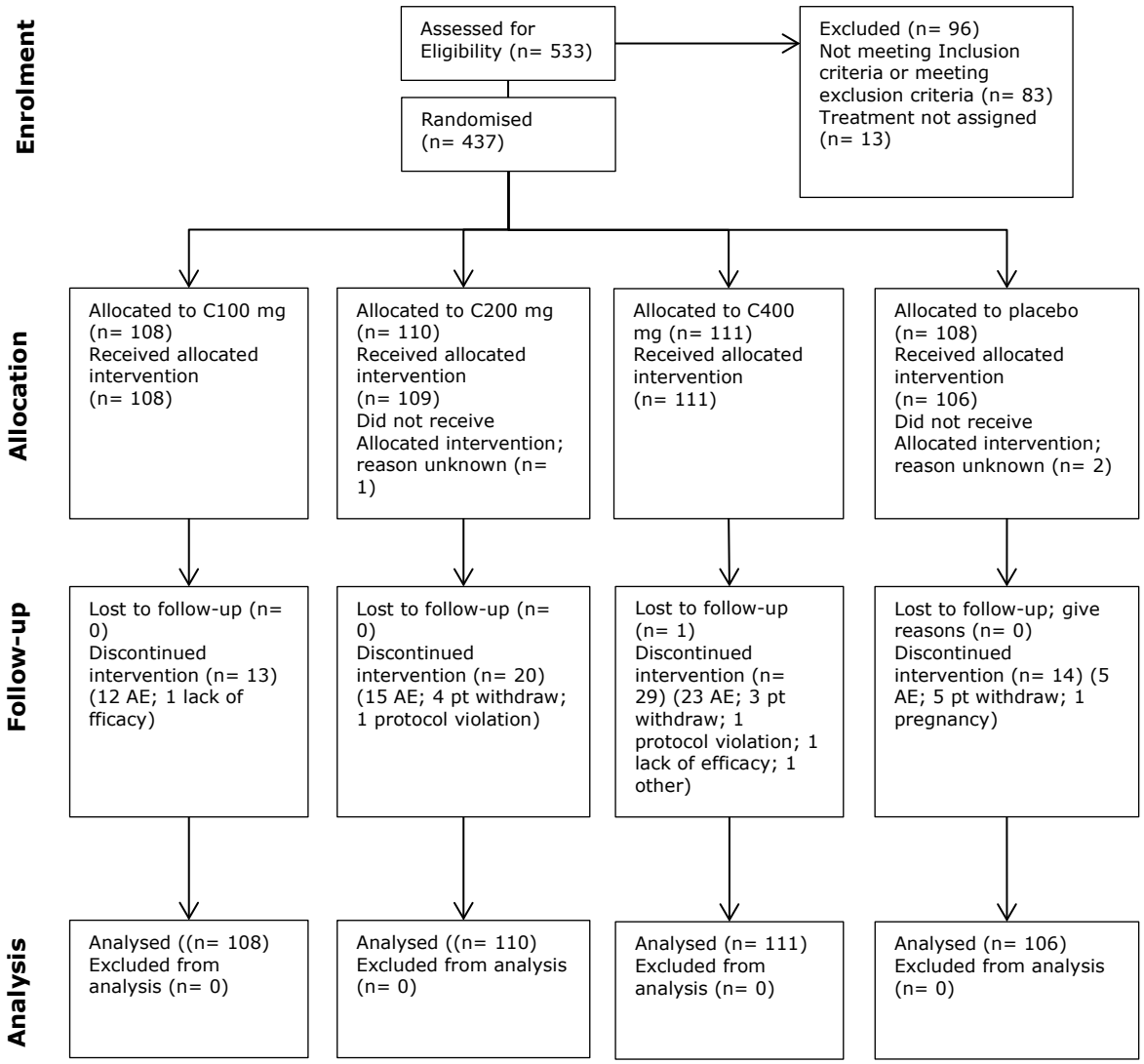
For the primary endpoint (≥50% responder rate), days with missing data were assumed to have the same seizure rate as days with non-missing data. To assess the effect of other potential seizure rate patterns and missing data during the maintenance phase on this efficacy endpoint analysis, several sensitivity analyses were conducted. These sensitivity analyses involved observed data from (1) the first 6 weeks of the maintenance phase and (2) the last 6 weeks of the maintenance phase.

The definition of the primary efficacy endpoint in the US and ROW (secondary endpoint in Europe) implicitly accounted for missing data in that it was identical to a definition in which days with missing data were assumed to have the same seizure rate as days with non-missing data.

Results

Participant flow

Figure 25



Conduct of the study

Two protocol amendments were made to the original protocol:

Amendment 1: with the following major changes:

• Reduced the initial starting dose to 50 mg/day and slowed the titration rate to improve tolerability.

• Clarified the definition of uncontrolled (focal) onset seizures.

• Provided guidance on contraception for male subjects.

• Allowed the first dose of study drug to be given at the investigator's site.

• Revised the timelines for the data monitoring committee review of data.

• Added a 50 mg/day dosing card.

Amendment 2: with the following major changes:

• Removed interim analysis.

• Provided details of proposed statistical procedures.

• Added lacosamide as one of the concomitant ASMs in the pharmacokinetic (PK) analysis.

Protocol deviations:

Almost all protocol deviations were classified as minor deviations and 16 major deviations were identified.

Baseline data

The main baseline data of C017 are summarised in the following tables:

Demographics and baseline characteristics

Table 10: Demographics and baseline characteristics; Study C017 (ITT for the Double-Blind)

	C100	C200	C400	Placebo
Patients, n	108	109	111	106
Age [years]				
Mean (SD)	39.0 (12.1)	40.9 (12.4)	39.6 (10.3)	39.5 (12.44)
Median (range)	37.5 (19, 66)	41.0 (19, 69)	38.0 (21, 66)	38.0 (19, 70)
Sex, n (%)				
Male	57 (52.8)	54 (49.5)	52 (46.8)	56 (52.8)
Female	51 (47.2)	55 (50.5)	59 (53.2)	50 (47.2)
Race, n (%)				
Caucasian	89 (82.4)	93 (85.3)	96 (86.5)	91 (85.8)
Black/African American	4 (3.7)	3 (2.8)	1 (0.9)	4 (3.8)
Asian	10 (9.3)	11 (10.1)	11 (9.9)	9 (8.5)
Other	5 (4.6)	2 (1.8)	3 (2.7)	2 (1.9)
Unknown	0	0	0	0
Weight [kg], mean (SD)	76.5 (18.1)	75.67 (18.2)	75.0 (19.2)	79.0 (23.6)
BMI [kg/m^2], mean (SD)	26.0 (5.4)	26.0 (5.4)	25.8 (4.9)	27.4 (7.9)

Source data: Additional Analyses Table 1.2

Epilepsy Disease Characteristics

Table 11: Epilepsy history

	C100	C200	C400	Placebo
Patients, n	108	109	111	106
Seizure frequency per 28 days at baseline				
Mean (SD)	21.5 (33.1)	30.6 (60.9)	24.1 (63.1)	25.3 (71.9)
Median (range)	9.5 (3.5, 202.0)	11.0 (4.0, 418.0)	9.0 (4.0, 638.0)	8.4 (4.0, 704.0)
Time since epilepsy diagnosis (years)				
Mean (SD)	25.4 (13.1)	22.7 (13.3)	24.9 (14.1)	23.2 (14.2)
Median (range)	23.0 (1, 62)	23.0 (1, 55)	24.0 (1, 59)	22.0 (1, 54)
Seizure types by history[1], n (%)				
Simple (focal aware)	23 (21.3)	20 (18.3)	24 (21.6)	24 (22.6)
Simple (focal aware)	25 (23.1)	25 (22.9)	22 (19.8)	22 (20.8)
Complex (focal unaware)	89 (82.4)	83 (76.1)	88 (79.3)	82 (77.4)
Secondary generalisation (focal to bilateral tonic-clonic) seizures	69 (63.9)	60 (55.0)	72 (64.9)	59 (55.7)
Generalised	6 (5.6)	2 (1.8)	4 (3.6)	6 (5.7)
Clusters	0	1 (0.9)	0	0
Other	0	2 (1.8)	0	2 (1.9)
Baseline ASMs[2], n (%)				
1 ASM	16 (14.8)	24 (22.0)	13 (11.7)	16 (15.1)
2 ASMs	43 (39.8)	42 (38.5)	44 (39.6)	42 (39.6)
3 ASMs	45 (41.7)	40 (36.7)	52 (46.8)	46 (43.4)
>3 ASMs	4 (3.7)	3 (2.8)	2 (1.8)	2 (1.9)

[1] Multiple answers were possible.

[2] ASMs started prior to and ongoing at the time of the first dose in the DB period.

Source data: Additional analyses report Tables 1.2, 1.8.1

Demographics and epilepsy disease characteristics in patient subgroups

Table 12: Failed ASMs

	C100	C200	C400	Placebo
Patients, n (%)	108	109	111	106
Failed ASMs/patient, mean (SD)	4.9 (3.25)	4.5 (3.24)	4.4 (3.00)	5.1 (3.58)
Failed ASMs/patient, median (range)	4 (1-17)	3 (1-16)	3 (1-15)	4 (1-18)
Failed ASMs/patient in categories, n (%)				
0	0	0	0	0
1	7 (6.5)	11 (10.1)	6 (5.4)	6 (5.7)
2	18 (16.7)	19 (17.4)	23 (20.7)	16 (15.1)
3	23 (21.3)	30 (27.5)	37 (33.3)	30 (28.3)
>3	60 (55.6)	49 (45.0)	45 (40.5)	54 (50.9)

Source data: Additional analyses report Table 1.26.3

Table 13: Concomitant ASMs, by category

	C100	C200	C400	Placebo
Patients, n (%)	108 (100.0)	109 (100.0)	111 (100.0)	106 (100.0)
Baseline ASMs[2], n (%)				
1 ASM	16 (14.8)	24 (22.0)	13 (11.7)	16 (15.1)
2 ASMs	43 (39.8)	42 (38.5)	44 (39.6)	42 (39.6)
3 ASMs	45 (41.7)	40 (36.7)	52 (46.8)	46 (43.4)
>3 ASMs	4 (3.7)	3 (2.8)	2 (1.8)	2 (1.9)
Concomitant ASM Category (ASM Type Subgroup Analysis)				
GABA modulators, n (%)	43 (39.8)	50 (45.9)	59 (53.2)	50 (47.2)
SCBs, n (%)	93 (86.1)	85 (78.0)	93 (83.8)	89 (84.0)
Carbamazepine, n (%)	29 (26.9)	31 (28.4)	26 (23.4)	38 (35.8)
Lamotrigine, n (%)	44 (40.7)	28 (25.7)	36 (32.4)	31 (29.2)
Benzodiazepines, n (%)	26 (24.1)	19 (17.4)	31 (27.9)	24 (22.6)
Levetiracetam, n (%)	47 (43.5)	48 (44.0)	51 (45.9)	40 (37.7)

GABA modulators: felbamate, phenobarbital, valproate, topiramate, tiagabine, tiagabine hydrochloride, vigabatrin, valproate magnesium, valproate semisodium, valproic acid, valproate sodium, ergenyl chrono.

SCBs: carbamazepine, oxcarbazepine, lamotrigine, lacosamide, eslicarbazepine, eslicarbazepine acetate.

Benzodiazepines: diazepam, clonazepam, clobazam, lorazepam, alprazolam, clorazepate dipotassium, clorazepic acid, lormetazepam, midazolam, midazolam hydrochloride, midazolam maleate, nitrazepam.

Source data: Additional analyses report, Tables 1.2 and 1.2.8 to 1.2.11

Numbers analysed

Figure 26: Number of Subjects

	YKP3089 (100 mg qd) n (%)	YKP3089 (200 mg qd) n (%)	YKP3089 (400 mg qd) n (%)	Placebo qd n (%)
Randomized	108 (100)	110 (100)	111 (100)	108 (100)
ITT population[a]	108 (100)	110 (100)	111 (100)	108 (100)
MITT population[a]	108 (100)	109 (99.1)	111 (100)	106 (98.1)
MITT-M population[a]	102 (94.4)	98 (89.1)	95 (85.6)	102 (94.4)
PP population[a]	97 (89.8)	99 (90.0)	97 (87.4)	105 (97.2)
SE population[a]	108 (100)	110 (100)	111 (100)	108 (100)
Completed double-blind treatment period[a]	95 (88.0)	90 (81.8)	81 (73.0)	94 (87.0)
Discontinued double-blind treatment period[a]	13 (12.0)	20 (18.2)	30 (27.0)	14 (13.0)
Entered open-label extension[a]	95 (88.0)	90 (81.8)	80 (72.1)	91 (84.3)

Abbreviations: ITT = intention-to-treat; MITT = modified intention-to-treat; MITT-M = MITT subjects in maintenance phase; PP = per protocol; qd = once daily; SE = safety evaluable.

Notes: The ITT population includes all randomized subjects; MITT population includes all randomized subjects with at least 1 dose of YKP3089 or placebo and any postbaseline seizure data; MITT-M population includes all randomized subjects who completed the titration phase, took at least 1 dose of YKP3089 or placebo in the maintenance phase and had maintenance phase seizure data; PP population includes all randomized subjects with no major protocol deviations, and had at least 80% compliance with study.

The SE population was the same as the ITT population.

[a] Percentages are based on the number of randomized subjects in each group.

Outcomes and estimation

Primary Outcome

Table 14: Responder rate, defined as at least 50% reduction in seizure frequency in the 12-week maintenance phase (ITT of the Maintenance)

	C100	C200	C400	Placebo
Patients	102	98	95	102
Responder	41 (40.2)	55 (56.1)	61 (64.2)	26 (25.5)
Nonresponder	61 (59.8)	43 (43.9)	34 (35.8)	76 (74.5)
p-value vs placebo[1]	0.036	<0.001	<0.001	-

[1] Fisher's exact test

Source data: C017, Table 14.2.1.2.1

Secondary Outcomes

Table 15: Responder rate, defined as at least 50% reduction in seizure frequency in the 18-week DB period; (ITT of the Double-Blind)

	C100	C200	C400	Placebo
Patients	108	109	111	106
Responder	44 (40.7)	63 (57.8)	67 (60.4)	23 (21.7)
Nonresponder	64 (59.3)	46 (42.2)	44 (39.6)	83 (78.3)
p-value vs placebo[1]	0.003	<0.001	<0.001	-

[1] Fisher's exact test

Source data: C017, Table 14.2.2.1.1

Table 16: Responder rates, based on 75%, 90% or 100% reduction in seizure frequency in the 12-week maintenance phase (ITTs of the Maintenance)

	C100	C200	C400	Placebo
12-Week maintenance phase				
Patients	102	98	95	102
Responder (≥75%)	17 (16.7)	28 (28.6)	43 (45.3)	10 (9.8)
p-value[1]	0.215	0.001	<0.001	-
Responder (≥90%)	9 (8.8)	17 (17.3)	27 (28.4)	3 (2.9)
p-value[1]	0.134	<0.001	<0.001	-
Responder (100%)	4 (3.9)	11 (11.2)	20 (21.1)	1 (1.0)
p-value[1]	0.369	0.002	<0.001	-

[1] Fisher's exact test of the respective cenobamate dose group vs placebo

Source data: Additional analyses report Table 8.2

Table 17: Percent change from baseline in seizure frequency in the 12-week maintenance phase

	C100		C200		C400		Placebo	
	Absolute	CFB	Absolute	CFB	Absolute	CFB	Absolute	CFB
Baseline								
n	102	-	98	-	95	-	102	-
Mean (SD)	21.0 (31.3)	-	32.1 (63.9)	-	25.8 (68.0)	-	25.1 (73.1)	-
Median (range)	9.8 (3.5, 202.0)	-	12.0 (4.0, 418.0)	-	9.0 (4.0, 638.0)	-	8.1 (4.0, 704.0)	-
End of maintenance phase								
n	102	102	98	98	95	95	102	102
Mean (SD)	12.9 (21.9)	-33.4 (47.8)	26.4 (82.3)	-41.7 (57.6)	15.2 (54.8)	-53.1 (50.2)	21.3 (64.6)	-17.7 (62.6)
Median (range)	5.7 (0.0, 168.0)	-41.5 (-100.0, 150.0)	5.4 (0.0, 678.2)	-56.5 (-100.0, 188.0)	3.0 (0.0, 494.9)	-63.0 (-100.0, 133.0)	6.4 (0.0, 618.3)	-27.0 (-100.0, 282.0)
p-value vs placebo[1]	0.054		<0.001		<0.001		-	

Abbreviations: CFB= change from baseline
Negative numbers for CFB mean a reduction in seizure frequency from baseline.

[1] ANCOVA with terms for ranked baseline seizure rate and treatment

Source data: C017, Table 14.2.2.2.1

Sensitivity Analyses

During the assessment, the applicant was asked to perform a more conservative estimation of the treatment effect, based on the full MITT dataset and with methods for handling missing data that do not imply that do not assume continuing treatment effect such as copy increment from refence and jump to reference.

Although to a lesser extent, and only clinically significant for the 200 and 400 mg treatment arms, these analyses yielded results within the same magnitude of effect.

This indicates with a reasonable level of confidence that the population that did not reach the maintenance period for any reason, even if not responding well to cenobamate, would not significantly impact on the final results, accounting for both seizure counts: of the maintenance period only and of the entire DB period.

Figure 27

Table 1: C017 Seizure Frequency Rate per 28-day: ANCOVA of Log-Transformed Seizure Frequency in the 18-week Double-blind Period Using Observed Data, Jump To Reference and Copy Reference imputation methods (imputation via Multivariate Normal repeated measures model) Observed data: (Intent-to-Treat for the Maintenance Phase of Double-Blind Period) Jump To Reference and Copy Reference: (Intent-to-Treat for the Modified Double-Blind Period ITT of the Double Blind)

Analysis Type	Imputation Method	Treatment comparison	LS-Mean difference (95% CI)	Stderr (of LS-Mean difference)	Relative Reduction vs placebo [1] (95% CI)	P-value
Original Analysis – Maintenance ITT Population (N= 397)	Observed data	100 mg (N=102) vs Placebo (N = 102)	-0.30 (-0.59, -0.01)	0.15	26.04 (44.61, 1.23)	0.041
		200 mg (N=98) vs Placebo (N = 102)	-0.56 (-0.86, -0.27)	0.15	43.11 (57.56, 23.74)	<.001
		400 mg (N=95) vs Placebo (N = 102)	-0.99 (-1.29, -0.70)	0.15	62.91 (72.37, 50.21)	<.001
Sensitivity Analysis 1 – Modified ITT population (N = 434)	Jump to reference (Multivariate Normal repeated measures model)	100 mg (N=108) vs Placebo (N = 106)	-0.21 (-0.53, 0.11)	0.16	19.01 (41.07, -11.31)	0.194
		200 mg (N=109) vs Placebo (N = 106)	-0.50 (-0.83, -0.17)	0.17	39.33 (56.36, 15.64)	0.003
		400 mg (N=111) vs Placebo (N = 106)	-0.73 (-1.07, -0.38)	0.18	51.75 (65.80, 31.92)	<.001
Sensitivity Analysis 2 – Modified ITT population (N = 434)	Copy reference (Multivariate Normal repeated measures model)	100 mg (N=108) vs Placebo (N = 106)	-0.25 (-0.57, 0.06)	0.16	22.37 (43.52, -6.69)	0.119
		200 mg (N=109) vs Placebo (N = 106)	-0.55 (-0.87, -0.22)	0.17	42.03 (58.14, 19.70)	0.001
		400 mg (N=111) vs Placebo (N = 106)	-0.86 (-1.19, -0.52)	0.17	57.47 (69.65, 40.42)	<.001

Source: Day 180 Question 6 Table 1

[1] Relative reduction (%) vs placebo is calculated using as (1-ratio of the estimated seizure frequency per 28-day of each active group vs placebo which is calculated by exponentiating the LS-Mean difference)*100. Similar calculation is used for deriving the 95% confidence interval.

Ancillary analyses

Table 18: Responder rates, based on at least 50% and 100% reduction in seizure frequency during the 12-week maintenance phase by Seizure Type

	C100		C200		C400		Placebo	
	Patients, n	Responder, n (%)	Patients, n	Responder, n (%)	Patients, n	Responder, n (%)	Patients, n	Responder, n (%)
Type B (focal aware seizure)								
Responder (≥50%)	21	10 (47.6)	24	15 (62.5)	20	14 (70.0)	17	2 (11.8)
Responder (100%)	21	5 (23.8)	24	3 (12.5)	20	6 (30.0)	17	0
Type C (focal unaware seizure)								
Responder (≥50%)	95	41 (43.2)	87	46 (52.9)	86	55 (64.0)	87	28 (32.2)
Responder (100%)	95	5 (5.3)	87	14 (16.1)	86	22 (25.6)	87	2 (2.3)
Type D (secondarily generalised (focal to bilateral tonic-clonic) seizure)								
Responder (≥50%)	34	21 (61.8)	32	25 (78.1)	36	24 (66.7)	43	21 (48.8)
Responder (100%)	34	10 (29.4)	32	18 (56.3)	36	19 (52.8)	43	11 (25.6)

Source data: Additional analyses report, Table 10.2

Study 017: Percent change from baseline in seizure frequency per 28 days during the 12-week maintenance phase, by seizure type

Table 19: Percent Change from Baseline in Seizure Frequency per 28 days During the 12-week Maintenance Phase, by Seizure Type

	C100		C200		C400		Placebo	
	Absolute	CFB	Absolute	CFB	Absolute	CFB	Absolute	CFB
Type B – (focal aware) seizure								
Baseline								
n	21	-	24	-	20	-	17	-
Mean (SD)	29.2 (54.9)	-	42.5 (66.2)	-	25.1 (27.9)	-	59.1 (151.2)	-
Median (range)	6.5 (0.5, 187.0)	-	13.3 (0.5, 292.5)	-	15.0 (0.5, 103.5)	-	11.5 (1.5, 634.0)	-
Endpoint								
n	21	21	24	24	20	20	17	17
Mean (SD)	18.8 (38.7)	-47.4 (41.9)	40.6 (124.0)	-17.1 (126.8)	10.8 (19.6)	-43.1 (87.7)	53.5 (127.2)	33.8 (105.5)
Median (range)	3.6 (0.0, 168.0)	-48.8 (-100, 21.3)	9.2 (0.0, 616.0)	-60.3 (-100, 473.5)	1.9 (0.0, 77.5)	-78.5 (-100, 183.0)	15.5 (1.0, 538.0)	11.1 (-83.6, 345.5)
p-value vs placebo[1]		0.002		0.002		<0.001		
Type C – (focal unaware) seizure								
Baseline								
n	95	-	87	-	86	-	87	-
Mean (SD)	14.3 (16.8)	-	22.0 (51.5)	-	19.6 (68.8)	-	14.7 (22.5)	-
Median (range)	8.0 (0.5, 92.0)	-	8.0 (1.0, 418.0)	-	8.0 (0.5, 638.0)	-	8.0 (0.5, 153.0)	-
Endpoint								
n	95	95	87	87	86	86	87	87
Mean (SD)	8.7 (12.7)	-29.0 (58.2)	17.8 (50.2)	-42.6 (54.5)	11.0 (53.5)	-50.8 (64.1)	11.8 (21.6)	-19.5 (75.3)
Median (range)	4.6 (0.0, 75.7)	-40.4 (-100, 260.0)	3.3 (0.0, 338.8)	-53.8 (-100, 188.4)	2.4 (0.0, 494.9)	-70.5 (-100, 273.2)	5.0 (0.0, 165.7)	-33.5 (-100, 466.4)
p-value vs placebo[1]		0.309		0.003		<0.001		
Type D – secondary generalised (focal to bilateral tonic-clonic) seizure								
Baseline								
n	34	-	32	-	36	-	43	-
Mean (SD)	4.9 (6.6)	-	6.6 (12.8)	-	7.2 (17.6)	-	6.3 (19.8)	-
Median (range)	3.3 (0.5, 35.5)	-	2.8 (0.5, 71.0)	-	2.0 (0.5, 89.0)	-	2.5 (0.5, 131.5)	-
Endpoint								
n	34	34	32	32	36	36	43	43
Mean (SD)	2.5 (3.1)	-48.9 (57.6)	1.9 (4.5)	-60.9 (87.3)	7.7 (27.9)	-41.7 (108.3)	5.1 (18.5)	-35.5 (72.7)
Median (range)	1.7 (0.0, 14.2)	-60.9 (-100, 145.5)	0.0 (0.0, 23.4)	-100.0 (-100, 361.0)	0.0 (0.0, 144.0)	-100.0 (-100, 352.0)	1.3 (0.0, 122.1)	-47.6 (-100, 251.3)
p-value vs placebo[1]		0.301		0.003		0.040		

Negative numbers for CFB mean a reduction in seizure frequency from baseline.

[1] p-value is based on an analysis of covariance (ANCOVA) model fit to the ranked values of percent change in seizure frequency from baseline period with terms for ranked baseline seizure rate and randomised treatment group

Source data: Additional analyses report, Table 9.2

Table 20: Number of Patients Reporting Seizure Types During Maintenance Phase but not at Baseline

	C100	C200	C400	Placebo
Patients	102	98	95	102
Seizure Type B	2 (2.0)	1 (1.0)	0	1 (1.0)
Seizure Type C	0	1 (1.0)	1 (1.1)	3 (2.9)
Seizure Type D	8 (7.8)	2 (2.0)	6 (6.3)	4 (3.9)

Source data: Additional analyses report Table 11.2

Table 21: Responder rate, defined as at least 50% reduction in seizure frequency in the 12-week maintenance period, in subgroups defined by demographics and by region

	C100		C200		C400		Placebo	
	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)
Sex								
Male	55	18 (32.7)	49	27 (55.1)	44	32 (72.7)	55	12 (21.8)
Female	47	23 (48.9)	49	28 (57.1)	51	29 (56.9)	47	14 (29.8)
Age								
18-64 years	100	40 (40.0)	95	54 (56.8)	94	60 (63.8)	98	24 (24.5)
≥65 years	2	1 (50.0)	3	1 (33.3)	1	1 (100.0)	4	2 (50.0)
Race								
Caucasian	84	35 (41.7)	86	45 (52.3)	84	53 (63.1)	87	24 (27.6)
Non-Caucasian	18	6 (33.3)	12	10 (83.3)	11	8 (72.7)	15	2 (13.3)
Region								
USA	26	9 (34.6)	20	13 (65.0)	23	13 (56.5)	26	6 (23.1)
Europe	57	24 (42.1)	60	31 (51.7)	60	38 (63.3)	58	18 (31.0)
Asia	10	4 (40.0)	10	8 (80.0)	7	6 (85.7)	9	1 (11.1)
ROW	9	4 (44.4)	8	3 (37.5)	5	4 (80.0)	9	1 (11.1)

Source data: ISE Tables 5.2.1 to 5.2.4

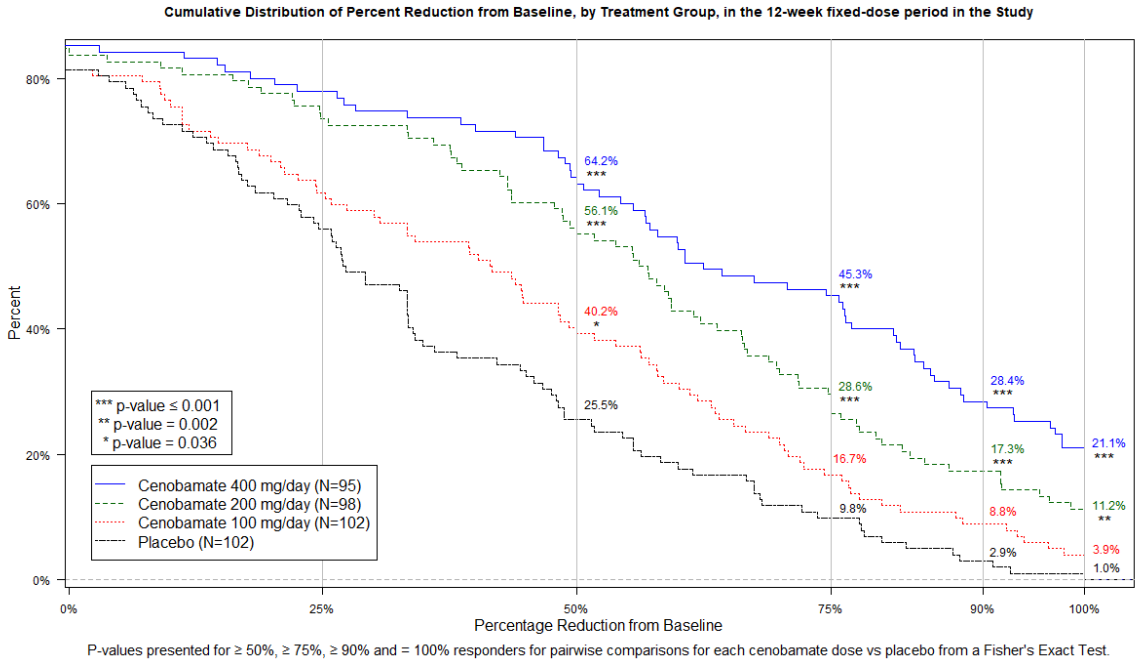
Table 22: Responder rate, defined as at least 50%, 75%, 90% and 100% reduction in seizure frequency in the 12-week maintenance period, in subgroups defined by concomitant ASM use

	C100		C200		C400		Placebo	
	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)	Patients, n	Responders, n (%)
SCBs								
Yes ≥50%	88	31 (35.2)	75	38 (50.7)	80	51 (63.8)	86	23 (26.7)
Yes ≥75%	88	13 (14.8)	75	17 (22.7)	80	34 (42.5)	86	9 (10.5)
Yes ≥90%	88	7 (8.0)	75	11 (14.7)	80	20 (25.0)	86	2 (2.3)
Yes 100%	88	2 (2.3)	75	7 (9.3)	80	14 (17.5)	86	1 (1.2)
GABA modulator								
Yes ≥50%	41	21 (51.2)	45	27 (60.0)	49	33 (67.3)	48	17 (35.4)
Yes ≥75%	41	9 (22.0)	45	17 (37.8)	49	27 (55.1)	48	6 (12.5)
Yes ≥90%	41	4 (9.8)	45	11 (24.4)	49	18 (36.7)	48	2 (4.2)
Yes 100%	41	3 (7.3)	45	7 (15.6)	49	15 (30.6)	48	1 (2.1)
Benzodiazepines								
Yes ≥50%	23	10 (43.5)	16	6 (37.5)	25	19 (76.0)	22	4 (18.2)
Yes ≥75%	23	5 (21.7)	16	2 (12.5)	25	14 (56.0)	22	3 (13.6)
Yes ≥90%	23	4 (17.4)	16	2 (12.5)	25	8 (32.0)	22	1 (4.5)
Yes 100%	23	2 (8.7)	16	0	25	5 (20.0)	22	0
Levetiracetam								
Yes ≥50%	44	16 (36.4)	45	25 (55.6)	48	30 (62.5)	40	7 (17.5)
Yes ≥75%	44	5 (11.4)	45	13 (28.9)	48	24 (50.0)	40	2 (5.0)
Yes ≥90%	44	3 (6.8)	45	6 (13.3)	48	15 (31.3)	40	2 (5.0)
Yes 100%	44	2 (4.5)	45	5 (11.1)	48	12 (25.0)	40	1 (2.5)
Carbamazepine								
Yes ≥50%	28	9 (32.1)	28	16 (57.1)	20	15 (75.0)	36	6 (16.7)
Yes ≥75%	28	3 (10.7)	28	9 (32.1)	20	10 (50.0)	36	2 (5.6)
Yes ≥90%	28	1 (3.6)	28	6 (21.4)	20	7 (35.0)	36	1 (2.8)
Yes 100%	28	0	28	4 (14.3)	20	4 (20.0)	36	0
Lamotrigine								
Yes ≥50%	43	13 (30.2)	26	12 (46.2)	31	18 (58.1)	31	11 (35.5)
Yes ≥75%	43	5 (11.6)	26	4 (15.4)	31	12 (38.7)	31	3 (9.7)
Yes ≥90%	43	2 (4.7)	26	2 (7.7)	31	7 (22.6)	31	0
Yes 100%	43	1 (2.3)	26	1 (3.8)	31	6 (19.4)	31	0

Source data: Additional analyses report, Tables 8.2.1 to 8.2.8

Analysis of clinical information relevant to dosing recommendations

Figure 28



Exposure-response (efficacy) pharmacometric assessments

Summary of main study(ies)

The following Table 23 summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23: Summary of Efficacy for study C017

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of Cenobamate as Adjunctive Therapy in Subjects with Focal Onset Seizures, with Optional Open-Label Extension		
Study identifier	YKP3089C017EudraCT Number**:** 2013-001858-10 ClinicalTrials.gov Identifier: NCT01866111	
Design	Double-blind, multicentre, randomised, placebo-controlled study to investigate the effective dose range and safety of cenobamate as adjunctive therapy for the treatment of focal seizures.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	18-weeks (6-week titration and 12-week maintenance phase 8-week baseline period (no treatment) 12-month open-label extension phase. Participation in the open-label extension phase could continue if the subject was receiving a benefit until development is stopped

Hypothesis	Superiority vs placebo with step-down procedure testing: The 200 mg dosage group was compared with the placebo group at a 2-sided 0.05 level as the first step. If no statistically significant difference was detected between the 200 mg dosage group and the placebo group, the procedure was stopped, and it was concluded that none of the cenobamate dosages were efficacious. If a statistically significant difference was detected between the 200 mg dosage group and the placebo group in favour of the 200 mg dosage group, the procedure proceeded to the next step to compare the 400 mg dosage group with the placebo group at a 2-sided 0.05 level. If a statistically significant difference was detected between the 400 mg dosage group and the placebo group in favour of the 400 mg dosage group, the procedure proceeded to the next step to compare the 100 mg dosage group with the placebo group at a 2-sided 0.05 level.		
Treatments groups	C100mg		Cenobamate 100mg/day (in addition to stable background anti-epileptic drug (ASM) therapy for 18-weeks (including a 6-week titration phase and a 12-week maintenance phase), 108 patients randomised
	C200mg		Cenobamate 200mg/day (in addition to stable background ASM therapy) for 18-weeks (including a 6-week titration phase and a 12-week maintenance phase), 110 patients randomised
	C400mg		Cenobamate 400mg/day (in addition to stable background ASM therapy) for 18-weeks (including a 6-week titration phase and a 12-week maintenance phase), 111 patients randomised
	PBO		Placebo tablets (in addition to stable background ASM therapy) for 18-weeks (including a 6-week titration phase and a 12-week maintenance phase), 108 patients randomised
Endpoints and definitions	Primary endpoint EU, Australia, New Zealand, South Africa	≥50% Focal Onset Seizure (FOS) Responder Rate Maintenance Phase	Responder rate defined as % of patients with ≥50% reduction in seizure frequency during the 12-week maintenance phase
	Primary endpoint US, rest of world (excluding EU, AUS, NZ, SA)	% change in FOS frequency DB	Percent change from baseline in seizure frequency per 28 days, 18-week DB period
	Secondary endpoint EU, Australia, New Zealand, South Africa	% change in FOS frequency Maintenance Phase	Percent change from baseline in seizure frequency per 28 days, 12-week maintenance phase
	Secondary endpoint EU, Australia, New Zealand, South Africa	≥75% ≥90% and 100% FOS Responder Rate Maintenance Phase	Responder rates defined on higher cut-offs as % of patients with ≥75%, 90%, or 100% reduction in seizure frequency during the 12-week maintenance phase

	Secondary Endpoint US, rest of world (excluding EU, AUS, NZ, SA)	≥50% FOS Responder Rate DB	Responder rate defined as % of patients with ≥50% reduction in seizure frequency during the 18-week DB period
	Post-hoc (Secondary)	% change in FOS frequency by seizure type Maintenance Phase	Percent change from baseline in seizure frequency per 28 days in the 12-week Maintenance Phase by seizure type (Type B focal aware seizure), Type C (focal unaware seizure), Type D (secondarily generalised, focal to bilateral tonic-clonic seizure))
	Post-hoc (Secondary)	≥50% FOS Responder Rate by seizure type Maintenance Phase	Responder rate (defined as patients with ≥50% reduction in seizure frequency during the 12-week maintenance phase) by seizure type (Type B (focal aware seizure), Type C (focal unaware seizure), Type D (secondarily generalised, focal to bilateral tonic-clonic seizure))
	Post-hoc (Secondary)	≥50% FOS Responder Rate by Concomitant ASM Use Maintenance Phase	Responder rate (defined as patients with ≥50% reduction in seizure frequency during the 12-week maintenance phase) by Concomitant ASM Use
	Post-hoc (Secondary)	≥50% FOS Responder Rate by # of Concomitant ASMs) Maintenance Phase	Responder rate (defined as patients with ≥50% reduction in seizure frequency during the 12-week maintenance phase) by number of Concomitant ASMs (1, 2, >2)
Database lock	25 Jan 2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Intent to treat of the 12-week maintenance phase (EU) (ITT of the Maintenance); 18- week double blind (US ROW) (ITT of the DB)		

Descriptive statistics and estimate variability	**Treatment group**	**C100 mg**	**C200mg**	**C400 mg**	**PBO**
	Number of subjects (ITT of the Maintenance)	102	98	95	102
	50% FOS Responder Rate Maintenance Phase, n (%)	41 (40.2)	55 (56.1)	61 (64.2)	26 (25.5)
	Number of subjects (ITT of the DB)	108	109	111	106
	≥50% FOS Responder Rate DB, n (%)	44 (40.7)	63 (57.8)	67 (60.4)	23 (21.7)
	Number of subjects (ITT of the DB)	108	109	111	106

% change in FOS frequency rate, DB (Median)	-35.5	-55.0	-55.0	-24.0
% change in FOS frequency rate min, max	-100, 206	-100, 191	-100, 167	-91, 198
Number of subjects (ITT of the Maintenance)	102	98	95	102
% change in FOS frequency rate, Maintenance Phase (Median)	-41.5	-56.5	-63.0	-27.0
% change in FOS frequency rate min max	-100,150	-100, 188	-100, 133	-100, 282
Number of subjects (ITT of the Maintenance)	102	98	95	102
≥75% Responder Rate Maintenance Phase	17 (16.7)	28 (28.6)	43 (45.3)	10 (9.8)
≥90% Responder Rate Maintenance Phase	9 (8.8)	17 (17.3)	27 (28.4)	3 (2.9)
100% Responder Rate Maintenance Phase	4 (3.9)	11 (11.2)	20 (21.1)	1 (1.0)
Number of subjects	21	24	20	17
% change in FOS frequency (Type B) Maintenance Phase (Median)	-48.8	-60.3	-78.5	11.1
Number of subjects	95	87	86	87
% change in FOS frequency (Type C) Maintenance Phase (Median)	-40.4	-53.8	-70.5	-33.5
Number of subjects	34	32	36	43
% change in FOS frequency (Type D) Maintenance Phase (Median)	-60.9	-100	-100	-47.6
Number of subjects	21	24	20	17
50% FOS Responder Rate (Type B) Maintenance Phase	10 (47.6)	15 (62.5)	14 (70.0)	2 (11.8)
Number of subjects	95	87	86	87
50% FOS Responder Rate (Type C) Maintenance Phase	41 (43.2)	46 (52.9)	55 (64.0)	28 (32.2)
Number of subjects	34	32	36	43

	50% FOS Responder Rate (Type D) Maintenance Phase	21 (61.8)	25 (78.1)	24 (66.7)	21 (48.8)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (SCB)	88 31 (35.2)	75 38 (50.7)	80 51 (63.8)	86 23 (26.7)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (GABA)	41 21 (51.2)	45 27 (60.0)	49 33 (67.3)	48 17 (35.4)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (Benzodiazepines)	23 10 (43.5)	16 6 (37.5)	25 19 (76.0)	22 4 (18.2)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (Levetiracetam)	44 16 (36.4)	45 25 (55.6)	48 30 (62.5)	40 7 (17.5)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (Carbamazepine)	28 9 (32.1)	28 16 (57.1)	20 15 (75.0)	36 6 (16.7)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (Lamotrigine)	43 13 (30.2)	26 12 (46.2)	31 18 (58.1)	31 11 (35.5)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (1 ASM)	15 6 (40.0)	22 13 (59.1)	12 8 (66.7)	15 3 (20.0)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (2 ASM)	42 16 (38.1)	37 23 (62.2)	36 22 (61.1)	41 12 (29.3)
	Number of subjects 50% FOS Responder Rate Maintenance Phase (>2 ASM)	45 19 (42.2)	39 19 (48.7)	47 31 (66.0)	46 11 (23.9)
Effect estimate per comparison	Primary endpoint 50% FOS Responder Rate Maintenance Phase	Comparison groups		(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO	
		Proportion of Responders (active, placebo)		(1) 40.2%, 25.5% (2) 56.1%, 25.5% (3) 64.2%, 25.5%	
		Variability statistic		Not included in CSR analysis.	

		P-value	(1) 0.036 (2) <0.001 (3) <0.001
	Secondary endpoint Median % change in FOS frequency DB	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO
		Median % change (active, placebo)	(1) -35.5%, -24.0% (2) -55.0%, -24.0% (3) -55.0%, -24.0%
		Variability statistic	Not included in CSR analysis.
		P-value	(1) 0.007 (2) <0.001 (3) <0.001
	Secondary endpoint Median % change in FOS frequency Maintenance Phase	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO
		Median % change (active, placebo)	(1) -41.5%, -27.0% (2) -56.5%, -27.0% (3) -63.0%, -27.0%
		Variability statistic	Not included in CSR analysis.
		P-value	(1) 0.054 (2) <0.001 (3) <0.001
	Secondary endpoint ≥75% ≥90% and 100% FOS Responder Rate Maintenance	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO
		Proportion of Responders (active, placebo)	≥75% (1) 16.7%, 9.8% (2) 28.6%, 9.8% (3) 45.3%, 9.8% ≥90% (1) 8.8%, 2.9% (2) 17.3%, 2.9% (3) 28.4%, 2.9% 100% (1) 3.9%, 1.0% (2) 11.2%, 1.0% (3) 21.1%, 1.0%
		Variability statistic	Not included in CSR analysis.
		P-value	≥75%: (1) 0.215 (2) 0.001 (3) <0.001 ≥90% (1) 0.134 (2) <0.001 (3) <0.001 100% (1) 0.369 (2) 0.002 (3) <0.001
	% reduction in FOS frequency by seizure type Maintenance Phase	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO

		Median % change (active, placebo)	Type B (1) -48.8%, 11.1% (2) -60.3%, 11.1% (3) -78.5%, 11.1% Type C (1) -40.4%, -33.5% (2) -53.8%, -33.5% (3) -70.5%, -33.5% Type D (1) -60.9%, -47.6% (2) -100.0%, -47.6% (3) -100.0%, -47.6%
		Variability statistic	Not included in CSR analysis.
		P-value	Type B (1) 0.002 (2) 0.002 (3) <0.001 Type C (1) 0.309 (2) 0.003 (3) <0.001 Type D (1) 0.301 (2) 0.003 (3) 0.040
	≥50% FOS Responder Rate by seizure type Maintenance Phase	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO
		Proportion of Responders (active, placebo)	Type B (1) 47.6%, 11.8% (2) 62.5%, 11.8% (3) 70.0%, 11.8% Type C (1) 43.2%, 32.2% (2) 52.9%, 32.2% (3) 64.0%, 32.2% Type D (1) 61.8%, 48.8% (2) 78.1%, 48.8% (3) 66.7%, 48.8%
		Variability statistic	Not included in analysis.
		P-value	Type B (1) 0.034 (2) 0.001 (3) <0.001 Type C (4) 0.169 (5) 0.009 (6) <0.001 Type D (1) 0.357 (2) 0.016 (3) 0.171
	≥50% FOS Responder Rate by Concomitant ASM Use Maintenance Phase	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO

		Proportion of Responders (active, placebo)	SCB (1) 35.2%, 26.7% (2) 50.7%, 26.7% (3) 63.8%, 26.7% GABA (1) 51.2%, 35.4% (2) 60.0%, 35.4% (3) 67.3%, 35.4% Benzo (1) 43.5%, 18.2% (2) 37.5%, 18.2% (3) 76.0%, 18.2% Lev (1) 36.4%, 17.5% (2) 55.6%, 17.5% (3) 62.5%, 17.5% Carb (1) 32.1%, 16.7% (2) 57.1%, 16.7% (3) 75.0%, 16.7% Lam (1) 30.2%, 35.5% (2) 46.2%, 35.5% (3) 58.1%, 35.5%
		Variability statistic	Not included in CSR analysis.
		P-value	Not included in analysis.
	≥50% FOS Responder Rate by # of Concomitant ASMs) Maintenance Phase	Comparison groups	(1) C100mg vs PBO (2) C200mg vs PBO (3) C400mg vs PBO
		Proportion of Responders (active, placebo)	1 ASM (1) 40.0%, 20.0% (2) 59.1%, 20.0% (3) 66.7%, 20.0% 2 ASM (1) 38.1%, 29.3% (2) 62.2%, 29.3% (3) 61.1%, 29.3% >2 ASM (1) 42.2%, 23.9% (2) 48.7%, 23.9% (3) 66.0%, 23.9%
		Variability statistic	Not included in analysis.
		P-value	Not included in analysis.
Analysis description	**Primary Analysis**		
	The EU primary efficacy endpoint was based on the MITT-M population for the 12-week maintenance period. Data were analysed by a Chi-square test. A step-down procedure was used to ensure the type I error rate due to multiple treatment comparisons was controlled at the 5% level. The study was planned and powered based on the primary efficacy endpoint defined for the US and ROW, i.e. percent change from baseline in seizure frequency per 28 days in the DB period. This analysis was performed based on the ITT for the DB period. The primary efficacy analysis used a non-parametric (ranked) analysis of covariance (ANCOVA) model with terms for ranked baseline seizure rate and treatment.		
Analysis description	**Secondary and Post-hoc Analysis**		

	The EU secondary efficacy endpoint was the percent change from baseline in seizure frequency per 28 days in the 12-week maintenance phase, based on the ITT for the maintenance phase. The analysis model was the same as defined for the US primary endpoint. Responder rates defined by higher cut-offs (patients with ≥75%, ≥90%, or 100% reduction in seizure frequency during the 12-week maintenance phase based on the ITT of the maintenance period) were analysed using Fisher's exact test without the step-down procedure for testing dose levels vs placebo. Median percentage change for focal seizure subtypes (including Type B focal aware seizure), Type C (focal unaware seizure), and Type D (secondarily generalised, focal to bilateral tonic-clonic seizure) was summarised using descriptive statistics. Responder rates are also presented descriptively by subgroups of Concomitant ASM.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Table 24: Age breakdown for patients ≥65 (including placebo)

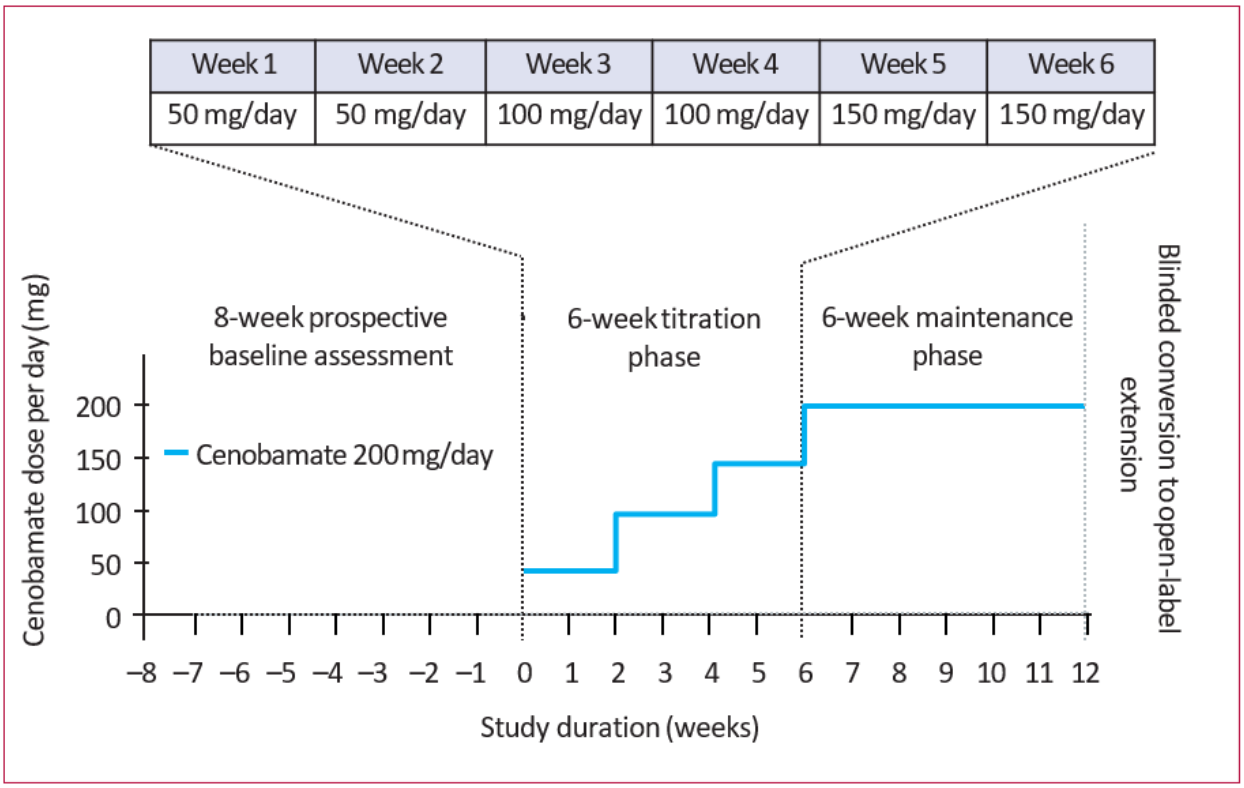
	Age 65-74 (Older subjects' number / total number)	**Age 75-84 (Older subjects' number / total number)**	**Age 85+ (Older subjects' number / total number)**
Phase 1 trials	29/ 67	3/ 67	0/ 67
Controlled Trials	10/ 658	0/ 658	0/ 658
Non-Controlled trials	42/ 1340	0/ 1340	0/ 1340

Supportive study(ies)

Study C013: A Phase 2, multi-centre, double-blind, randomised, adjunctive placebo-controlled trial with an open-label extension to evaluate the efficacy and safety of cenobamate (YKP3089) in subjects with drug resistant focal onset seizures

Study C013 Design

Figure 29



Primary objective: To evaluate the efficacy of cenobamate 200 mg in reducing seizure frequency in patients with focal onset seizures (focal seizures) not fully controlled despite treatment with 1 to 3 concomitant ASMs.

Methods: Adult patients were eligible if they had a history of epilepsy for at least 2 years; a diagnosis of treatment resistant focal epilepsy according to ILAE criteria; at least 3 focal aware onset seizures or (focal unaware) or secondarily generalised (focal to bilateral tonic-clonic) seizures per month with no consecutive 21-day seizure-free period. Patients had to be on stable doses of 1-3 ASMs for at least 12 weeks before randomisation.

Dose reductions could occur at any visit and during any of the study periods (i.e. titration, maintenance, or OLE). Patients who had their dose increased in a scheduled titration step and subsequently failed to meet tolerability criteria had to have their dose decreased. Patients who were unable to tolerate 50 mg were to discontinue treatment at the discretion of the investigator. Dose increases after prior dose reductions were not allowed.

Efficacy assessments were based on the seizure diary, at weekly intervals during the titration period and 2-weekly intervals during the maintenance phase. ASM use was recorded at 2-weekly intervals during the titration period and after the second and sixth week of the maintenance phase. Samples were taken to measure cenobamate and ASM levels.

The primary efficacy endpoint of the study was the percent change in seizure frequency per 28 days from baseline during the treatment period; the secondary efficacy endpoint was the responder rate (defined as patients with a reduction of ≥50% in seizure frequency in the treatment period).

Results: A total of 222 patients were randomised into the study (200 mg/day: n=113; placebo: n=109). Of these, equal proportions (200 mg/day: 90.3%; placebo: 90.8%) completed the DB period; the most frequent reasons for non-completion were withdrawal by the patient (4.4% vs 3.7%) and AEs (3.5% vs 3.7%). Equal proportions of patients (67.3% vs 67.0%) entered the OLE period.

About half of the randomised patients were female (200 mg/day: 51.3%; placebo: 46.8%). Mean (SD) age was 36.9 years. About half of the patients were White/Caucasian (200 mg/day: 50.4%, placebo: 53.2%), and Asians accounted for the second-largest race group (43.4% vs 41.3%).

The median number of seizures per 28 days at baseline was 7.5 in the cenobamate 200 mg group and 5.5 in the placebo group. The median time since epilepsy diagnosis was 239 vs 253 months, equivalent to about 23 years in either group. About half of patients (46.9% vs 48.1%) had 2 baseline ASMs, and 26.3% vs 41.7% had more than 2 ASMs. Less than 20% of patients in either arm had only one baseline ASM.

In the cenobamate 200 mg group, median seizure frequency decreased from 7.5 during the baseline period to 3.8 during the DB period, the median reduction was 55.6%. In the placebo group, the median seizure frequency decreased from 5.5 during the baseline period to 5.0 during the DB period (-21.5%). The difference was statistically significant ($p<0.0001$).

Considering only the maintenance phase, median seizure frequency per 28 days decreased in the cenobamate 200 mg group from 7.6 at baseline to 2.8 (-45.%) and in the placebo group from 5.5 at baseline to 4.6 (-15.9%) ($p<0.0001$).

The responder rate in the DB period was statistically significantly ($p<0.0001$) higher in the cenobamate 200 mg group (50.4%) than in the placebo group (22.2%).

Overall, 8.8% of patients receiving cenobamate 200 mg reached freedom from seizures in the DB period, vs 0.9% of placebo patients. Considering only the maintenance phase, 28.3% of patients in the cenobamate group became seizure free, vs 8.8% of patients receiving placebo.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Two double-blind studies, C013 and C017, were provided in this submission.

The study C017 is considered as main clinical study. Its design was adequate for a dose finding phase 2 study. Since it was upgraded to a pivotal study, there was some discussions to ensure that it fulfilled the relevant guidelines, including the requirements of the 'Points to consider on application with one pivotal study' (CPMP/EWP/2330/99). In particular, it was noted that, although the number of missing data increases significantly with the dose (23% for 400 mg arm, 9.5% for 100 mg and 15-5% for 200 mg as compared to 8.5% for placebo) the ITT results do not significantly differ from M-ITT results presented with the initial submission. Further additional analyses, including composite strategy estimand considering those with less than 50% improvement and all missed evaluations as a non-responder, were also provided. The CHMP agreed that these additional analyses were satisfactory and confirmed the magnitude of treatment benefit and robustness of results.

In the original C017 protocol, the initial titration to the maintenance dose was rapid, with increments of 100 mg. This led to a high discontinuation rate (10.5%) due to adverse events (see also clinical safety discussion). The titration was consequently revised to a slower titration (1st protocol amendment). The CHMP agreed that this correction occurred early in the study and that the consequences of the quick titration do not seem to impact the results.

The study C017 included mostly EU patients (57.6%). A geographical analysis of data was performed and showed no significant differences which confirmed the robustness of results.

Both studies enrolled a significantly diseased population, many with drug-resistant epilepsy and multiple treatment failures. Inclusion and exclusion criteria were adequate. It is however noted that patients older than 65 years of age were only included in Study C017 with 10 patients ≥65 years of age (9 in the maintenance phase population).

Efficacy data and additional analyses

Based on the percentage of responders, the magnitude of the clinical effect was clear: 56.1% of subjects treated with cenobamate 200 mg and 64.2% with cenobamate 400 mg were responders (having at least 50% reduction in seizure frequency) in comparison to 25.5% with placebo. This means that the therapeutic effect on the proposed dose is > 25% of seizure frequency reduction. This is clinically relevant, particularly in an uncontrolled population with most of them fulfilling the criteria for drug-resistant epilepsy. The lower 100mg dose also had a slight effect.

In addition, the CHMP noted that 11.2% of subjects treated with cenobamate 200 mg and 21.1% with cenobamate 400 mg showed 100% response (i.e. were seizure free) in comparison with 1.0% with placebo. This 100% response effect rarely occurs with other antiepileptic drugs in this population (uncontrolled patients who have failed a median of 4 ASMs in the past).

The analyses of the entire double-blind period, including up titration, show the same trend (57.8% with cenobamate 200mg, 60.4% with 400mg vs. 21.7% with placebo with ≥50% reduction in seizure frequency) indicating that the clinical effect starts early during titration.

The effect of cenobamate over the different types of seizures (focal aware, focal unaware and secondarily generalised, focal to bilateral tonic-clonic seizures) is also clinically relevant: all 3 cenobamate treatment groups (100mg, 200mg and 400mg/day) significantly reduced focal aware seizure frequency during the double-blind treatment period. The 200 mg/day and 400 mg/day treatment groups significantly reduced the focal unaware seizures and secondarily generalised, focal to bilateral tonic-clonic seizures per 28 days during the double-blind treatment period.

There seemed to be a less significant effect on patients treated with benzodiazepines(clobazam) and lamotrigine, requiring higher doses of cenobamate to achieve similar 50% reduction responses. An overall decreased effect when cenobamate was added to lamotrigine was observed. Whilst it could not be fully clarified, the CHMP agrees with the SmPC recommendation that dose of cenobamate may need to be increased depending on individual response when co-administered with lamotrigine.

No clinically relevant quality of life changes were demonstrated. In the study C017, the measurement of the quality of life with QOLIE-31-P was limited to only English-speaking countries and this decreased the sample considerably (n=133 at baseline compared to n=434 at baseline in MITT).

The results of the supportive study C013 align with those of the main study C017 and support the proposed target dose.

It was noted that the clinical studies included only a small number of patients >65 years of age (10 patients in study C017) and it was therefore not possible to determine whether they responded differently from younger patients.

Dose-response relationship

A clear dose-response relationship was observed between doses of 100, 200 and 400 mg of cenobamate and magnitude of response.

In order to support the target dose of 200 mg/day (maximum of 400 mg/day), an exposure-response relationship defined by a population PD model describing the relationship between AUC and seizure

count was presented (SK16008). The model-based results supports a continued increment in efficacy up to the maximum therapeutic dose of 400 mg/day, based on the decrease in weekly seizure count that was evident with increasing doses (100 to 600 mg/day) and the simulated fraction of patients with more than 50% reduction in seizure frequency. These data are in line with the clinical efficacy data from Study C017 study, which also showed that median seizure frequency was significantly lower for cenobamate 200 mg (-56.5%) and 400 mg (-63%), compared to placebo. Overall, the totality of the data supports that a notable number of patients achieve key clinical improvement and seizure freedom at doses up to 200 mg/day. Modal analyses of dose by study support the need for doses higher than 200 mg/day in some patients for appropriate long-term effectiveness. The information is correctly reflected in the agreed posology recommendation (section 4.1 of the SmPC).

2.5.4. Conclusions on the clinical efficacy

The efficacy of cenobamate, in the claimed indication, is supported by 2 randomised, double-blind studies (main study C17 and supportive study C013). In both studies, cenobamate treatment was associated with a reduction of seizures frequency. The CHMP agreed that the available data support the efficacy of the use of cenobamate as adjunctive treatment of focal onset seizures in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least 2 ASMs.

2.6. Clinical safety

Patient exposure

A total of 2564 subjects were exposed to cenobamate in the 26 clinical studies.

Considering the significant differences between study designs and exposures to cenobamate and in order to have a comprehensive review of cenobamate safety, 5 analysis populations for patients/subjects who received at least one dose of cenobamate were established. These populations took into consideration the type of study they were selected from: DB Pool, LT OLE Pool, Phase 2/3 Pool, C021, and Phase 1 Pool. Additionally, a separate analysis was done for each of the studies C013 and C017.

Table 25: Analysis populations used for this Summary of Clinical Safety

Analysis population	Abbreviated Name	Patients/Subjects Included	Studies Included	Number of Patients/Subjects
Pooled Double-Blind	DB Pool	Patients exposed to cenobamate or placebo during the double-blind period	C013 DB C017 DB	Cenobamate N=442 Placebo N=216[1]
Double-Blind Study C017	Study C017	Patients exposed to cenobamate or placebo during the double-blind period	C017	Cenobamate N=329 Placebo N=108[1]
Double-Blind Study C013	Study C013	Patients exposed to cenobamate or placebo during the double-blind period	C013	Cenobamate N=113 Placebo N=109
Long-Term Open-Label Extension[2]	LT OLE Pool	Patients who completed DB period and continued in the OLE extension	C013 OLE C017 OLE	Total N=504 Placebo in DB to cenobamate in OLE, N=163 Continued on cenobamate in OLE, N=341
Long-Term Open-Label Study C021	Study C021	Patients who received at least 1 dose of cenobamate Cenobamate + Phenytoin (N=83); Cenobamate + Phenobarbital (N=37); Cenobamate + Other ASMs (N=1220)	C021	Total N=1340
All Patients Exposed to Cenobamate in Phase 2 and 3 Studies[2]	Phase 2/3 Pool	Patients exposed to cenobamate (received at least 1 dose) irrespective of study design or period (i.e., DB or OLE)	C013, DB and OLE C017, DB and OLE C021	Total N=1945 N=186 N=419 N=1340
Phase 1 Pool[3]	Phase 1 Pool	Subjects who received at least 1 dose of cenobamate		Total N=619 (607 Phase 1, 12 Phase 2a)
			AA40616[4]	N=12
			AA22780	N=77
			AA24143	N=35
			AA39450	N=16
			AA41857	N=6
			YKP3089C006	N=28
			YKP3089C009	N=14
			YKP3089C010	N=16
			YKP3089C011	N=12
			YKP3089C014	N=15
			YKP3089C016	N=16
			YKP3089C018	N=21
			YKP3089C019	N=14
			YKP3089C020	N=54
			YKP3089C022	N=16
			YKP3089C024	N=48
			YKP3089C026	N=24
			YKP3089C027	N=24
			YKP3089C028	N=31
			YKP3089C029	N=30
			YKP3089C030	N=26
			YKP3089C031	N=24
			YKP3089C032	N=60

The mean duration of exposure to cenobamate was 15.1 weeks for the DB pool and up to 192.6 weeks in the LT OLE subgroups.

Adverse events

Study C017

Figure 30: Summary of Treatment-Emergent Adverse Events (Safety Evaluable Population, Double-Blind Treatment Period)

	Number (%) of Subjects			
	YKP3089 100 mg (N=108)	YKP3089 200 mg (N=110)	YKP3089 400 mg (N=111)	Placebo (N=108)
Subjects with TEAEs	70 (64.8)	84 (76.4)	100 (90.1)	76 (70.4)
Subjects with treatment-related TEAEs	62 (57.4)	72 (65.5)	92 (82.9)	46 (42.6)
Subjects who died due to a TEAE	0	0	0	0
Subjects discontinued due to a TEAE	11 (10.2)	15 (13.6)	22 (19.8)	5 (4.6)
Subjects with serious TEAEs	10 (9.3)	4 (3.6)	8 (7.2)	6 (5.6)

Most Common Adverse Events

Figure 31: Treatment-Emergent Adverse Events (All Causalities) by System Organ Class and Preferred Term in at least 5% of Subjects in Any Treatment Group by Descending Order (Safety Evaluable Population, Double-Blind Treatment Period)

System Organ Class MedDRA Preferred Term	Number (%) of Subjects			
	YKP3089 100 mg (N=108)	YKP3089 200 mg (N=110)	YKP3089 400 mg (N=111)	Placebo (N=108)
Subjects with at least 1 TEAE	70 (64.8)	84 (76.4)	100 (90.1)	76 (70.4)
Nervous system disorders	48 (44.4)	56 (50.9)	80 (72.1)	34 (31.5)
Somnolence	20 (18.5)	23 (20.9)	41 (36.9)	9 (8.3)
Dizziness	19 (17.6)	22 (20.0)	37 (33.3)	15 (13.9)
Headache	11 (10.2)	12 (10.9)	12 (10.8)	6 (5.6)
Balance disorder	3 (2.8)	2 (1.8)	10 (9.0)	0
Nystagmus	3 (2.8)	4 (3.6)	7 (6.3)	1 (0.9)
Ataxia	2 (1.9)	4 (3.6)	7 (6.3)	1 (0.9)
Dysarthria	2 (1.9)	3 (2.7)	7 (6.3)	0

General disorders and administration site conditions	17 (15.7)	25 (22.7)	40 (36.0)	17 (15.7)
Fatigue	13 (12.0)	19 (17.3)	27 (24.3)	9 (8.3)
Gait disturbance	1 (0.9)	6 (5.5)	9 (8.1)	3 (2.8)
Eye disorders	12 (11.1)	14 (12.7)	21 (18.9)	5 (4.6)
Diplopia	8 (7.4)	11 (10.0)	17 (15.3)	2 (1.9)
Gastrointestinal disorders	19 (17.6)	13 (11.8)	27 (24.3)	10 (9.3)
Constipation	2 (1.9)	3 (2.7)	10 (9.0)	1 (0.9)
Nausea	7 (6.5)	1 (0.9)	10 (9.0)	1 (0.9)
Vomiting	2 (1.9)	3 (2.7)	6 (5.4)	0
Injury, poisoning, and procedural complications	10 (9.3)	15 (13.6)	13 (11.7)	14 (13.0)
Fall	2 (1.9)	4 (3.6)	4 (3.6)	6 (5.6)
Infections and infestations	14 (13.0)	20 (18.2)	17 (15.3)	21 (19.4)
Upper respiratory tract infection	3 (2.8)	4 (3.6)	3 (2.7)	6 (5.6)
Musculoskeletal and connective tissue disorders	6 (5.6)	5 (4.5)	11 (9.9)	12 (11.1)
Back pain	4 (3.7)	1 (0.9)	6 (5.4)	3 (2.8)
Ear and labyrinth disorders	1 (0.9)	3 (2.7)	7 (6.3)	3 (2.8)
Vertigo	1 (0.9)	3 (2.7)	6 (5.4)	3 (2.8)
Metabolism and nutrition disorders	5 (4.6)	3 (2.7)	7 (6.3)	3 (2.8)
Decreased appetite	3 (2.8)	1 (0.9)	6 (5.4)	1 (0.9)

Figure 32: Treatment-Emergent Adverse Events by Maximum Intensity (Safety Evaluable Population, Double-Blind Treatment Period)

	Number (%) of Subjects			
Severity	**YKP3089 100 mg (N=108)**	**YKP3089 200 mg (N=110)**	**YKP3089 400 mg (N=111)**	**Placebo (N=108)**
Mild	27 (25.0)	39 (35.5)	29 (26.1)	40 (37.0)
Moderate	32 (29.6)	34 (30.9)	53 (47.7)	28 (25.9)
Severe	11 (10.2)	11 (10.0)	18 (16.2)	8 (7.4)

Figure 33: Severe Treatment-Emergent Adverse Events by Preferred Term Occurring in 2 or More Subjects in Any Treatment Group (Safety Evaluable Population, Double-Blind Treatment Period)

	Number (%) of Subjects			
System Organ Class Preferred Term	**YKP3089 100 mg (N=108)**	**YKP3089 200 mg (N=110)**	**YKP3089 400 mg (N=111)**	**Placebo (N=108)**
Subjects with at least 1 severe TEAE	11 (10.2)	11 (10.0)	18 (16.2)	8 (7.4)
Nervous system disorders	5 (4.6)	6 (5.5)	13 (11.7)	3 (2.8)
Dizziness	2 (1.9)	3 (2.7)	3 (2.7)	2 (1.9)
Somnolence	0	2 (1.8)	7 (6.3)	0
Ataxia	1 (0.9)	0	2 (1.8)	0
Balance disorder	1 (0.9)	0	2 (1.8)	0

Study C013

Figure 34: Overall Summary of Adverse Events – Safety Population, Double-Blind Treatment Period

	YKP3089 (N=113)	Placebo (N=109)
	n (%)	n (%)
Subjects with TEAEs	86 (76.1)	69 (63.3)
Subjects with treatment-related TEAEs	67 (59.3)	50 (45.9)
Subjects who died due to a TEAE	0	0
Subjects discontinued due to an TEAE	5 (4.4)	3 (2.8)
Subjects with serious TEAEs	2 (1.8)	4 (3.7)

Most common adverse events

Figure 35: Treatment-Emergent AEs Occurring at >=5% in Either Treatment Group by System Organ Class and Preferred Term – Safety Population, Double- Blind Treatment Period

MedDRA System Organ Class Preferred Term	YKP3089 (N=113) n (%)	Placebo (N=109) n (%)
Subjects with TEAEs	86 (76.1)	69 (63.3)
Gastrointestinal disorders	26 (23.0)	13 (11.9)
Constipation	6 (5.3)	0
Diarrhea	6 (5.3)	0
Nausea	13 (11.5)	5 (4.6)
Vomiting	6 (5.3)	2 (1.8)
General Disorders and Administration Site Conditions	19 (16.8)	17 (15.6)
Fatigue	12 (10.6)	7 (6.4)
Infections and Infestations	27 (23.9)	15 (13.8)
Nasopharyngitis	7 (6.2)	1 (0.9)
Upper respiratory tract infection	8 (7.1)	5 (4.6)
Urinary tract infection	9 (8.0)	2 (1.8)
Nervous System Disorders	58 (51.3)	43 (39.4)
Balance disorder	9 (8.0)	1 (0.9)
Dizziness	25 (21.1)	18 (16.5)
Headache	14 (12.4)	14 (12.8)
Nystagmus	11 (9.7)	0
Somnolence	25 (22.1)	13 (11.9)
Tremor	7 (6.2)	3 (2.8)
Psychiatric Disorders	13 (11.5)	13 (11.9)
Anxiety	1 (0.9)	6 (5.5)

Severity of adverse events

Among subjects treated with cenobamate, 45 (39.8%) subjects had mild TEAEs, 39 (34.5%) subjects had moderate TEAEs, and 2 (1.8%) subjects had severe TEAEs. Among placebo treated subjects, 36

(33.0%) subjects had mild TEAEs, 26 (23.9%) subjects had moderate TEAEs, and 7 (6.4%) subjects had severe TEAEs.

The severe TEAEs in the cenobamate 200 mg group were urinary tract infection (150 mg) and tooth extraction (100 mg). In the placebo group, severe events were status epilepticus, convulsions, dizziness, pyrexia, vomiting, GERD, diplopia, and dizziness.

DB Pool

The median duration of exposure to cenobamate was 17.86 weeks, and 85.5% of patients received cenobamate for ≥12 weeks. Overall exposure to cenobamate totalled 127.8 person- years. Most patients experienced an AE, with a larger proportion of the cenobamate group experiencing treatment-related AEs (64.5% vs. 44.0% receiving placebo). The most common AEs in patients receiving cenobamate were somnolence (24.7% vs. 10.2% receiving placebo), dizziness (23.3% vs. 15.7%), fatigue (16.1% vs. 7.4%), and headache (11.3% vs. 9.3%) with most events occurred during the titration phase.

Most AEs were either mild or moderate (36.2% and 25.0%) in severity; the frequency of moderate AEs increased with cenobamate dose. The only severe AEs reported in >1% of patients receiving cenobamate were somnolence (2.0% vs. 0%) and dizziness (1.8% vs. 1.9% in placebo). The frequency of severe AEs increased with dose for vertigo, fatigue, somnolence, dysarthria and headache. 64.5% of patients receiving cenobamate experienced at least 1 AE that was considered related to the study drug by the investigator.

Vertigo, nausea, constipation, vomiting, fatigue, gait disturbance, somnolence, dizziness, balance disorder, and ataxia incidence generally increased with cenobamate dose.

AEs that occurred at a notably higher frequency (≥5%) across all cenobamate dose groups compared with placebo included diplopia, fatigue and somnolence.

The most common treatment-related AEs were somnolence (23.8% of patients vs. 9.3% in the placebo group), dizziness (21.0% vs. 13.4%) and fatigue (15.6% vs. 7.4%) which were also dose dependent.

A larger proportion of patients receiving cenobamate experienced an AE that led to study drug discontinuation (13.1% vs. 4.2% in the placebo group), such as ataxia, dizziness, somnolence, vertigo, and nystagmus, with a dose dependency.

No deaths were reported in the DB.

A comparable proportion of patients receiving cenobamate and placebo experienced SAEs and severe AEs and at least 1 study drug-related SAE.

A larger proportion of patients receiving cenobamate underwent dose reduction due to an AE (18.1% vs. 6.5% in the placebo group), also related to higher cenobamate exposure doses. The most frequent AEs that led to study drug dose reduction were dizziness, somnolence and diplopia.

The cenobamate 400 mg group had a slightly higher proportion of patients with severe AEs and AEs that led to study drug or study discontinuation.

LT OLE population:

Figure 36: Adverse events occurring in >5% of patients in any treatment group by preferred term – LT OLE Pool

System organ class Preferred term	Number (%) of Patients All Cenobamate (N=504)	Cenobamate DB to cenobamate OLE (N=341)	Placebo DB to cenobamate OLE (N=163)
Patients with at least 1 AE	446 (88.5)	301 (88.3)	145 (89.0)
Nervous system disorders	**331 (65.7)**	**221 (64.8)**	**110 (67.5)**
Dizziness	171 (33.9)	116 (34.0)	55 (33.7)
Somnolence	119 (23.6)	69 (20.2)	50 (30.7)
Headache	94 (18.7)	63 (18.5)	31 (19.0)
Seizure	35 (6.9)	23 (6.7)	12 (7.4)
Balance disorder	31 (6.2)	18 (5.3)	13 (8.0)
Nystagmus	30 (6.0)	19 (5.6)	11 (6.7)
Ataxia	24 (4.8)	15 (4.4)	9 (5.5)
Memory impairment	22 (4.4)	19 (5.6)	3 (1.8)
Infections and infestations	**204 (40.5)**	**134 (39.3)**	**70 (42.9)**
Upper respiratory tract infection	62 (12.3)	41 (12.0)	21 (12.9)
Viral upper respiratory tract infection	58 (11.5)	39 (11.4)	19 (11.7)
Urinary tract infection	38 (7.5)	23 (6.7)	15 (9.2)
General disorders and administration site conditions	**158 (31.3)**	**110 (32.3)**	**48 (29.4)**
Fatigue	72 (14.3)	48 (14.1)	24 (14.7)
Gait disturbance	48 (9.5)	35 (10.3)	13 (8.0)
Gastrointestinal disorders	**139 (27.6)**	**90 (26.4)**	**49 (30.1)**
Nausea	40 (7.9)	21 (6.2)	19 (11.7)
Vomiting	30 (6.0)	20 (5.9)	10 (6.1)
Injury, poisoning and procedural complications	**122 (24.2)**	**87 (25.5)**	**35 (21.5)**
Fall	41 (8.1)	25 (7.3)	16 (9.8)
Contusion	28 (5.6)	22 (6.5)	6 (3.7)
Ligament sprain	14 (2.8)	4 (1.2)	10 (6.1)
Eye disorders	**115 (22.8)**	**74 (21.7)**	**41 (25.2)**
Diplopia	65 (12.9)	42 (12.3)	23 (14.1)
Vision blurred	27 (5.4)	14 (4.1)	13 (8.0)
Musculoskeletal and connective tissue disorders	**96 (19.0)**	**66 (19.4)**	**30 (18.4)**
Back pain	35 (6.9)	25 (7.3)	10 (6.1)
Arthralgia	19 (3.8)	9 (2.6)	10 (6.1)
Ear and labyrinth disorders	**52 (10.3)**	**25 (7.3)**	**27 (16.6)**
Vertigo	35 (6.9)	17 (5.0)	18 (11.0)

Study C021 (Phase 3 multi-centre, open label study, Study treatment given on top of ≥1 ASMs)

Figure 37: Adverse events occurring in >5% of patients in any treatment group by preferred term (Study C021)

System organ class Preferred term	Number (%) of Patients Cenobamate (N=1340)	Cenobamate and phenytoin (N=83)	Cenobamate and phenobarbital (N=37)	Cenobamate and other AEDs (N=1220)
Patients with at least 1 AE	1185 (88.4)	72 (86.7)	35 (94.6)	1078 (88.4)
Nervous system disorders	**865 (64.6)**	**49 (59.0)**	**25 (67.6)**	**791 (64.8)**
Somnolence	405 (30.2)	21 (25.3)	17 (45.9)	367 (30.1)
Dizziness	359 (26.8)	28 (33.7)	13 (35.1)	318 (26.1)
Headache	208 (15.5)	6 (7.2)	7 (18.9)	195 (16.0)
Balance disorder	89 (6.6)	10 (12.0)	3 (8.1)	76 (6.2)
Seizure	74 (5.5)	3 (3.6)	3 (8.1)	68 (5.6)
Ataxia	59 (4.4)	6 (7.2)	3 (8.1)	50 (4.1)
Tremor	41 (3.1)	3 (3.6)	2 (5.4)	36 (3.0)

Dysarthria	38 (2.8)	1 (1.2)	3 (8.1)	34 (2.8)
Nystagmus	36 (2.7)	6 (7.2)	1 (2.7)	29 (2.4)
Infections and infestations	**468 (34.9)**	**30 (36.1)**	**17 (45.9)**	**421 (34.5)**
Viral upper respiratory tract infection	118 (8.8)	7 (8.4)	4 (10.8)	107 (8.8)
Upper respiratory tract infection	104 (7.8)	8 (9.6)	4 (10.8)	92 (7.5)
Urinary tract infection	57 (4.3)	7 (8.4)	2 (5.4)	48 (3.9)
Influenza	47 (3.5)	4 (4.8)	2 (5.4)	41 (3.4)
General disorders and administration site conditions	**409 (30.5)**	**25 (30.1)**	**13 (35.1)**	**371 (30.4)**
Fatigue	252 (18.8)	18 (21.7)	10 (27.0)	224 (18.4)
Gait disturbance	67 (5.0)	7 (8.4)	3 (8.1)	57 (4.7)
Gastrointestinal disorders	**354 (26.4)**	**21 (25.3)**	**13 (35.1)**	**320 (26.2)**
Nausea	108 (8.1)	5 (6.0)	0 (0.0)	103 (8.4)
Diarrhoea	70 (5.2)	4 (4.8)	4 (10.8)	62 (5.1)
Constipation	69 (5.1)	2 (2.4)	2 (5.4)	65 (5.3)
Psychiatric disorders	**310 (23.1)**	**20 (24.1)**	**8 (21.6)**	**282 (23.1)**
Anxiety	45 (3.4)	4 (4.8)	2 (5.4)	39 (3.2)
Injury, poisoning, and procedural complications	**279 (20.8)**	**17 (20.5)**	**10 (27.0)**	**252 (20.7)**
Fall	67 (5.0)	5 (6.0)	2 (5.4)	60 (4.9)
Toxicity to various agents	10 (0.7)	8 (9.6)	1 (2.7)	1 (0.1)
Musculoskeletal and connective tissue disorders	**192 (14.2)**	**12 (14.5)**	**7 (18.9)**	**173 (14.2)**
Back pain	41 (3.1)	3 (3.6)	2 (5.4)	36 (3.0)
Pain in extremity	18 (1.3)	1 (1.2)	2 (5.4)	15 (1.2)
Eye disorders	**185 (13.8)**	**12 (14.5)**	**5 (13.5)**	**168 (13.8)**
Diplopia	95 (7.1)	6 (7.2)	2 (5.4)	87 (7.1)
Vision blurred	62 (4.6)	4 (4.8)	3 (8.1)	55 (4.5)
Metabolism and nutrition disorders	**116 (8.7)**	**10 (12.0)**	**2 (5.4)**	**104 (8.5)**
Decreased appetite	41 (3.1)	5 (6.0)	1 (2.7)	35 (2.9)
Reproductive system and breast disorders	**60 (4.5)**	**3 (3.6)**	**2 (5.4)**	**55 (4.5)**
Erectile dysfunction	5 (0.4)	1 (1.2)	2 (5.4)	2 (0.2)

Impact of titration schemes on adverse event profile.
Different titration schemes were used in the clinical studies:

- Study C013: a slow titration rate was used (starting daily dose of 50 mg/day cenobamate or placebo with increases by 50 mg/day increments every 2 weeks, based on tolerability of treatment, to a cenobamate target dose of 200 mg/day over a 6-week titration phase - treatment continued for a subsequent 6-week maintenance phase).

- Study C017: a more rapid titration schedule was used (starting dose of 100 mg/day, with a weekly increase of 100 mg/day until the target dose was reached). Due to early issues with tolerability, after 46 patients (10.5%) were treated under the initial rapid titration scheme, the titration schedule was adapted: the starting dose became 50 mg/day, and the titration rate was 50 mg/day per week until a daily dose of 200 mg/day was reached, with subsequent 100-mg/day-increments for patients with a target dose of 400 mg/day).

- Study C021: a slower titration schedule was used (starting dose of 12.5 mg/day, increased to 25 mg/day after 2 weeks and then 50 mg day after 2 weeks. Patients were then up titrated by 50 mg/day every 2 weeks to a target of 200 mg/day and could increase to a maximum dose of 400 mg/day).

Figure 38: 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.

All 3 DRESS cases occurred in studies that had rapid titration to target dose.

Rash/hypersensitivity reactions were associated with higher initial doses and/or dosing intervals of cenobamate with no differences among placebo arms of different studies.

Severity of AEs, percentage of AEs leading to discontinuation, and SAEs were higher for subjects on cenobamate titrated weekly compared to those titrated every other week in the DB Pool.

The AEs that were notably more frequent in patients titrated weekly were fatigue and diplopia (also more frequent in the cenobamate arm and showing a dose-dependent increase in frequency).

Vital signs and physical findings:

Vital signs parameters (respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, and body temperature) were evaluated and data across studies have shown no noteworthy trends over time or meaningful differences between treatment groups. There were also no clinically relevant changes in body weight.

QT shortening

In the DB Pool and OLE Pool, there were no relevant changes in mean ECG parameters from baseline, and no relevant differences between treatment groups. Additionally, there was no relevant difference in the occurrence of cardiac events seen between groups.

- DB Pool: some patients had changes in QTcF from baseline of >30 ms, but none had changes of >60 ms. Palpitations were the most reported cardiac AE.

- study C017: several patients had QTcF values of <360 ms, but none had values of <340 ms. No patient had QTcF values of >500 ms, and none had QTcF changes from baseline of >60 ms. Cardiac disorder AEs were seen in some patients (bradycardia and sinus bradycardia in 1 patient each receiving cenobamate 200 mg; palpitations in both patients receiving cenobamate 400 mg; and sinus bradycardia and tachycardia in 1 patient each receiving placebo)

- study C013: Several patients had QTcF values <360 ms, but none had values <340 ms. No patient had QTcF values of >500 ms, and none had QTcF changes from baseline of >60 ms. Cardiac disorder AEs were reported for 3 cenobamate patients (2.7%) and 2 placebo patients (1.8%).

- OLE Pool: there were no patients with QTcF >500 ms in the OLE periods of the pivotal studies. One patient had a reported change from baseline QTcF of >60 ms in the cenobamate DB to OLE group at 12 months. Some patients had clinically significant abnormal ECGs but no trend was found. Cardiac disorder AEs occurred in 3.6% of patients overall, including 3.2% of patients taking cenobamate and 4.3% of patients taking placebo in the preceding DB period.

- C021: there were slight decreases in mean HR and in QTcF by 12 and 24 months after the start of treatment in Study C021. There were no relevant differences in HR between groups. For QTcF, changes appeared most pronounced in the cenobamate + phenytoin group at 24 months. Cardiac disorder AEs occurred in 26 patients overall (1.9%). With the exception of 1 patient (1.2%) who received cenobamate with phenytoin (who had congestive cardiac failure), all patients with cardiac disorder AEs received cenobamate with other ASMs.

In the cenobamate double-blind and long-term open label study subjects with cardiac past medical history were included however those with severe disease were excluded. Nevertheless 5.7% and 5.9% of cenobamate treated subjects had a prior medical history of cardiac disorders in the DB pool and in study C021 respectively. Over 90% of patients with cardiac history were able to complete the double-blind studies. The vast majority of patients remain in the study at the time of data cut-off (82.9%). Of the patients who discontinued, only 3 discontinued due to adverse events ("rash maculopapular," "fatigue" and "psychosis and suicide attempt.").

The incidence of subjects with cardiac disorder TEAEs across the cenobamate and placebo groups was comparable.

In long-term open label studies, 3 cases of cardiovascular AEs with an outcome of death occurred in subjects taking cenobamate for at least 1 year and 11 months. Additionally, cardiac disorder SAEs occurred in 2 elderly subjects in long-term open label studies after at least 6 months of treatment.

Overdose, drug abuse and dependence, withdrawal

There were no intentional cases of cenobamate **overdose**. There was 7 cases of overdose or medication error reported as AEs in Phase 2/3 studies including 1 intentional overdose but related to other (unknown) medications and not cenobamate.

There were no reports of **misuse, abuse, diversion or dependence**. Some patients had potentially abuse-related AE like somnolence, dizziness and fatigue and most mild or moderate in severity. The rare cases of severe potentially abuse-related AE were mostly dizziness.

a) In the abuse/dependency study (Study YKP3089C024), alprazolam was selected as the comparator due to the potential for sedative effects seen with cenobamate and there were also no reports of misuse, abuse, diversion, or dependence. Somnolence was the most common potentially abuse-related AE, with the incidence increasing with cenobamate dose; however, the incidence was >2-fold lower than reported for both alprazolam doses. Euphoric mood was reported at a similar incidence following administration of both alprazolam doses and cenobamate 400 mg. There was however no reports of euphoric mood with cenobamate 200 mg. Most AEs were mild in severity and considered related to the study drug.

b) Potentially abuse-related TEAEs in single-dose, open-label or double-blind studies and multiple-dose, double-blind in healthy subjects showed no reports of misuse, abuse, diversion or dependence. No potentially abuse-related AEs were reported following single dose administration of cenobamate alone at doses ≤300 mg. Mild or moderate somnolence was reported following administration of cenobamate 750 mg (4 of 7 subjects, 57.1%)

c) There were no reports of misuse, abuse, diversion or dependence among subjects with hepatic or renal impairment (Studies YKP3089C027 and YKP3089C028).

The overall incidence of euphoria in the Phase 2/3 pool was very low (0.3%) and were not dose related.

Adverse events of special interest, including events of suicidal nature, selected adverse skin reactions, and DRESS (Drug reaction with eosinophilia and systemic symptoms), were evaluated.

Table 26

Event	Number (%) of Patients		
	DB (N=442)	Phase 2/3 (N=1945)	Phase 1 (N=619)
DRESS	0 (0.0)	1 (0.1)	2 (0.4)
Skin reactions	17 (3.8)	163 (8.4)	n/a
Suicidal behaviour / ideation / attempt AEs	7 (1.6)	37 (1.9)	1 (0.4)

Abbreviations: AE=adverse event; DB=double blind; DRESS=drug reaction with eosinophilia and systemic symptoms; N=analysis population.

Suicidal behaviour/ideation/attempt: There were two cases of completed suicide in the clinical trial database, the first patient (Study C013 OLE) after 132 days of cenobamate treatment and the second patient (Study C017 OLE) after 3.8 years of treatment. None of the two events were considered as causality related.

In Study C013, 9.7 % of subjects in the cenobamate group and 8.3% in the placebo group had history of a suicide related event while in study C017, 4.7 to 7.7% of subjects in the cenobamate groups and 9.4% of subjects in the placebo group had such suicide related event prior histories. No increased rate of suicide-related AEs or reports of suicidal ideation or behaviours in C-SSRS was seen in the cenobamate treated patients compared to placebo.

In the long-term open label studies (Studies C017, C013, and C021), 37 patients reported 41 events that were considered of suicidal nature.

Since the data cut-off date for the MAA submission (July 1, 2019), there have been 6 additional TEAEs of suicidal behaviour and ideation. Two cases were assessed as related to treatment. The dose was not changed in any of the 6 cases and resolved in all but one case.

Skin reactions: In the DB Pool, the overall proportions of patients experiencing skin reactions and those leading to discontinuation were comparable for patients receiving cenobamate and placebo. There was no overall increase with dose. In the Phase 2/3 Pool and Phase 1 Pool, overall, the most frequent skin reactions event that led to discontinuation were rash, contact dermatitis, and pruritis. There were no Grade 5 skin reactions and no reports of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). No increase in skin reaction TEAEs incidence was observed in relation to the duration of treatment.

DRESS: DRESS was reported in 3 subjects (1 patient with epilepsy and 2 healthy volunteers; 1 in phase 2/3 and 2 in phase 1 studies; 1 fatal outcome). All cases occurred in studies with rapid weekly titration scheduled.

Serious adverse event/deaths/other significant events

Study C017

Most SAEs were reported under the nervous system disorders SOC. Serious TEAEs were reported for 10 (9.3%), 4 (3.6%), 8 (7.2%), and 6 (5.6%) subjects in the 100 mg/day, 200 mg/day, 400 mg/day, and placebo treatment groups, respectively, during the double-blind treatment period. The most commonly reported SAE was seizure, which was reported in 4 subjects overall. No deaths occurred during the study.

Study C013

There was a total of 7 subjects with SAEs during the double-blind treatment period (4 with placebo, 2 with cenobamate, and 1 just after the end of the taper from cenobamate had status epilepticus). Of the 2 cenobamate subjects, 1 experienced a drug hypersensitivity and the other was admitted for a urinary tract infection that was considered unrelated to study treatment. Of the 4 placebo subjects, 2

had status epilepticus and the other had a major seizure attack. No deaths occurred during the DB treatment period.

Study C021

Overall 14.2% of patients experienced at least 1 SAE, with the proportions being comparable across treatment groups. Overall 3.1% of patients receiving experienced at least 1 treatment related SAE, with the proportions being comparable across treatment groups. The most common treatment-related SAEs were ataxia (0.4%), dizziness (0.3%), and seizure, somnolence and rash (each 0.2%).

Seven patients in Study C021 experienced an AE that resulted in death (with events comprising sudden death, sudden unexplained death in epilepsy, subdural haematoma, traumatic intracranial haemorrhage, laryngospasm). None of the deaths were considered related to the study medication.

Phase 1 Pool

Seven subjects (1.1%) experienced at least 1 SAE, with events by preferred term experienced by ≥2 subjects comprising DRESS and gunshot wound. One subject had a treatment-emergent AEs that led to death in Phase 1 study population, with the event comprising eosinophilic myocarditis that was associated with DRESS and considered possibly related to the study drug.

Laboratory findings

Study C017

Haematology

There were no remarkable median changes from baseline observed for any treatment group. However median change from baseline values for haemoglobin, leukocytes, neutrophils, and platelets tended to shift downwards at Visits 6 and 9 in the cenobamate treatment groups compared with placebo. Two TEAEs associated with haematology results were reported during the double-blind treatment period: anaemia (1 subject; 400 mg/day treatment group) and leukopenia (1 subject; 400 mg/day treatment group). Neither of the events was serious, nor did they lead to treatment discontinuation.

Clinical Chemistry

Clinical chemistry parameters were generally similar across treatment groups at baseline. There were no remarkable changes from baseline observed for any treatment group. However median values for ALT and alkaline phosphatase tended to be higher at Visits 6 and 9 in the 400 mg/day group compared with placebo. The most frequently reported TEAEs associated with changes in clinical chemistry parameters was 'ALT increased' and 'AST increased' reported in 4 and 3 subjects respectively in the 400 mg group. One subject in the 400 mg/day treatment group experienced serious TEAEs of ALT increased and AST increased on Study Day 42.

Electrocardiograms

During the double-blind treatment period, median changes in ECG parameters were small and generally similar between the treatment groups.

Two ECG abnormalities were reported as TEAEs (1 in placebo group, 1 in 200 mg/day treatment group). No subjects had a QTcF >500 msec reported, and 1 subject (placebo) had a QTcF >450 msec and <480 msec reported during the double-blind treatment period. There were no reports of QTcF changes from baseline ≥60 msec (either increase or decrease) during the double-blind treatment period.

Study C013

Haematology

Although some abnormal values were noted in haematology parameters, none was clinically significant. The following haematologic TEAEs were noted in subjects treated with cenobamate: WBC count decreased (n=1), neutrophil count decreased (n=2), and neutropenia (n=1). These were modest decreases, 20-30%, at 1 or 2 visits (Visits 8-10). Among subjects treated with placebo, 1 had a TEAE of leukopenia and another had a TEAE of neutrophil count decreased.

Clinical chemistry

Minor mean elevations of ALT were seen during the treatment period. One subject treated with cenobamate had TEAEs of ALT increased and AST increased. One subject treated with placebo had a TEAE of transaminases increased. One placebo subject had a TEAE of AST increased.

ECG

No clinically significant changes from baseline were seen in the ECG parameters.

LT OLE pool

Haematology parameter values at baseline were comparable across the LT OLE groups.

The haematocrit shifted to low values were seen in 8.7% of patients overall, while 4.8% of all patients had shifts to high haematocrit values including 5.5% of patients using placebo in the DB period. Leukocyte counts shifted to low values in 17.1% of all patients (15.2% of patients taking cenobamate in the DB period and 20.9% of those taking placebo in the DB period) and to high values in 7.3% of patients (no between-group difference). Neutrophil counts shifted to low values in 13.9% of patients and occurred more frequently in patients receiving placebo in the DB period (18.5% vs. 11.7% in patients receiving cenobamate in the DB period). Shifts to high neutrophil counts were seen in 8.5% of all patients, with no relevant between-group difference.

Study C021

Haematology parameters at baseline were comparable across groups for the different treatment groups in Study C021. Mean changes from baseline to the end of the titration period and over the maintenance phase were generally small and comparable between the groups. Decreases in mean platelet count were seen that appeared to be more pronounced in patients concomitantly using phenytoin or phenobarbital than in patients using other ASMs together with cenobamate. Small decreases in haemoglobin were seen in patients using cenobamate plus phenobarbital but not in the other patients.

Haematocrit shifted to low values in 5.6% of patients overall, while 6.7% of patients had shift to low values, with no relevant differences between groups. Leukocyte counts shifted to low values in 13.8% overall (no between-group differences) and to high values in 9.0% overall (9.4% with cenobamate + other ASMs, 4.9% with cenobamate + phenytoin, 2.7% with cenobamate + phenobarbital). Lymphocyte counts shifted to low values in 8.2% overall and to high values in 5.5% overall, with no relevant between-group differences. Neutrophil counts shifted to low values in 13.8% of patients, with no between-group differences; shifts to high neutrophil counts occurred in 9.9% of all patients (10.1% with cenobamate + other ASMs, 11.0% with cenobamate + phenytoin, 0.0% with cenobamate + phenobarbital). Platelet shifts to high counts were seen in 7.7% of all patients, with no differences between groups; while 5.6% of patients receiving cenobamate and phenobarbital (but none of the other groups) had shifts to low values.

QT shortening

In the DB Pool and OLE Pool, there were no relevant changes in mean ECG parameters from baseline, and no relevant differences between treatment groups. Additionally, there was no relevant difference in the occurrence of cardiac events seen between groups.

- DB Pool: some patients had changes in QTcF from baseline of >30 ms, but none had changes of >60 ms. Palpitations were the most reported cardiac AE.

- study C017: several patients had QTcF values of <360 ms, but none had values of <340 ms. No patient had QTcF values of >500 ms, and none had QTcF changes from baseline of >60 ms. Cardiac disorder AEs were seen in some patients (bradycardia and sinus bradycardia in 1 patient each receiving cenobamate 200 mg; palpitations in both patients receiving cenobamate 400 mg; and sinus bradycardia and tachycardia in 1 patient each receiving placebo)

- study C013: Several patients had QTcF values <360 ms, but none had values <340 ms. No patient had QTcF values of >500 ms, and none had QTcF changes from baseline of >60 ms. Cardiac disorder AEs were reported for 3 cenobamate patients (2.7%) and 2 placebo patients (1.8%).

- OLE Pool: there were no patients with QTcF >500 ms in the OLE periods of the pivotal studies. One patient had a reported change from baseline QTcF of >60 ms in the cenobamate DB to OLE group at 12 months. Some patients had clinically significant abnormal ECGs but no trend was found. Cardiac disorder AEs occurred in 3.6% of patients overall, including 3.2% of patients taking cenobamate and 4.3% of patients taking placebo in the preceding DB period.

- C021: there were slight decreases in mean HR and in QTcF by 12 and 24 months after the start of treatment in Study C021. There were no relevant differences in HR between groups. For QTcF, changes appeared most pronounced in the cenobamate + phenytoin group at 24 months. Cardiac disorder AEs occurred in 26 patients overall (1.9%). With the exception of 1 patient (1.2%) who received cenobamate with phenytoin (who had congestive cardiac failure), all patients with cardiac disorder AEs received cenobamate with other ASMs.

In the cenobamate double-blind and long-term open label study subjects with cardiac past medical history were included however those with severe disease were excluded. Nevertheless 5.7% and 5.9% of cenobamate treated subjects had a prior medical history of cardiac disorders in the DB pool and in study C021 respectively. Over 90% of patients with cardiac history were able to complete the double-blind studies. The vast majority of patients remain in the study at the time of data cut-off (82.9%). Of the patients who discontinued, only 3 discontinued due to adverse events ("rash maculopapular," "fatigue" and "psychosis and suicide attempt.").

The incidence of subjects with cardiac disorder TEAEs across the cenobamate and placebo groups was comparable.

In long-term open label studies, 3 cases of cardiovascular AEs with an outcome of death occurred in subjects taking cenobamate for at least 1 year and 11 months. Additionally, cardiac disorder SAEs occurred in 2 elderly subjects in long-term open label studies after at least 6 months of treatment.

Liver parameters

Liver parameters at baseline were comparable across treatment groups for the DB Pool. Mean ALT and AST tended to increase slightly to the end of the titration phase in cenobamate treatment groups, and the increase became greater with dose. This increase had disappeared by the end of the double-blind period. No relevant change in ALT or AST was seen in the placebo group. Mean ALKP increased in all cenobamate-treated patients both in the titration phase and the DB period overall, with no obvious

dose effect. No relevant change was seen in the placebo group. No relevant changes were seen for mean bilirubin levels.

Notable (>5% of patients) shifts from normal or low baseline values to high values at any time postbaseline were seen for ALT in 9.8% of cenobamate-treated patients but only 4.7% of the placebo group. For the cenobamate group, a dose effect was seen for the proportion of patients with shifts to high ALT values (6.5% with cenobamate 100 mg, 8.2% with 200 mg, 16.5% with 400 mg). Shifts to high ALKP values occurred in 6.9% of cenobamate-treated patients vs. 2.8% of placebo patients with no systematic dose effect. Shifts to high AST values occurred in 4.8% of cenobamate patients (1.9% with cenobamate 100 mg, 5.0% with cenobamate 200 mg, 7.3% with 400 mg) vs. 3.3% of the placebo group.

In the cenobamate 200 mg group, 7.3% of patients had shifts to low bilirubin values but there were no notable (>5%) shifts to low values for any other parameter or group.

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).

In LT OLE pool, liver parameters at baseline were comparable across treatment groups for the LT OLE Pool. Mean ALKP increased in all groups; it was already apparent at the start of the OLE period in patients taking cenobamate in the preceding DB period, while it occurred only during the OLE period in patients taking placebo in the preceding DB period. No relevant trends were seen for the other liver parameters. Notable (>5% of patients) shifts from normal or low baseline values to high values at any time post-baseline were seen for ALKP (17.7% overall) and AST (7.8%). Notable (>5% of patients) shifts from high or normal baseline values to low values at any time post-baseline were seen for bilirubin (9.3%), with higher proportions in patients receiving placebo in the preceding DB period (14.8%) than in those receiving cenobamate in the DB period (6.7%).

Alanine aminotransferase shifted to high values in 16.3% of patients and to low values in 9.9% of patients overall, with no relevant differences between groups.

Alanine aminotransferase increases of ≥3 ULN occurred in 0.8% of all patients, and AST increases of ≥3 ULN in 0.6% of patients. A single patient had bilirubin values ≥2 ULN.

In Study C021, liver parameters at baseline were generally comparable across treatment groups for the different treatment groups in Study C021. There was no relevant trend over time or for differences between the groups, although mean ALKP tended to increase from baseline to 12 months in patients receiving cenobamate plus other ASMs and in the total study population. Patients receiving cenobamate and phenytoin had slight mean ALKP decreases at each time point. No relevant trend was seen for ALKP in the cenobamate + phenobarbital group. Notable (>5% of patients) shifts from normal or low baseline values to high values at any time post-baseline were seen for ALKP (15.4% overall), with no relevant treatment differences. Alanine aminotransferase shifted to lower values in 20.7% of patients (21.4% with cenobamate + other ASMs, 12.2% with cenobamate + phenytoin, 16.7% with cenobamate + phenobarbital) and to higher values in 20.6% of patients (no relevant treatment differences). Aspartate aminotransferase shifted to lower values in 5.6% of patients (6.0% with cenobamate + other ASMs, 1.2% with cenobamate + phenytoin, 2.8% with cenobamate + phenobarbital) and to higher values in 10.3% of patients (no relevant treatment differences).

Alanine aminotransferase increases of ≥3 ULN occurred in 1.6% of cenobamate patients, and AST increases of ≥3 ULN occurred in 1.1 %. Two patients (0.1%) had bilirubin values ≥2 ULN.

Safety in special populations

In the Pooled DB dataset, only 10 subjects >65 years of age were identified, 6 of whom were randomised to cenobamate. A total of 87 patients >65 participated in All Phase 2/3 Pool and 51 subjects were >65 years of age at study entry.

When the larger dataset of 87 subjects was analysed (dataset for subjects >65 during study participation), the overall incidence of most SAE SOCs for the elderly group was comparable to that in the younger group. The incidence of the most common (>5%) TEAEs for subjects >65 years of age during study participation was comparable with younger age groups. Adverse events known to be related to ASM such as fatigue, gait disturbance, fall, ataxia, balance disorder, dizziness and somnolence occurred in both younger and older age groups. However, higher incidence was observed in subjects above 65 years of age.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

Potential drug-drug or drug-food PK interactions studies were performed in healthy subjects who received cenobamate co-administered with ASMs, oral contraceptives (OCs), and other medications, including bupropion (for CYP2B6), midazolam (for CYP3A), and omeprazole (for CYP2C19). In general, co-administration of cenobamate with ASMs, OCs, and other medications did not result, apparently, in safety concerns but might impact on therapeutic strategies. Because of an increase in systemic exposure of phenytoin or phenobarbital with cenobamate, dose of phenytoin or phenobarbital may need to be reduced in patients on concomitant cenobamate (see clinical pharmacology sections).

In the carbamazepine interaction study, reductions in carbamazepine systemic exposure were noted with coadministration of cenobamate and carbamazepine but no effect of carbamazepine on cenobamate exposure was observed. 16 subjects experienced a total of 94 treatment-emergent AEs; of these, 65 were mild, 29 were moderate, and there were no severe AEs. The most commonly reported AEs were headache (n=9), abdominal pain (n=8), and constipation (n=8). No deaths, SAEs, or AEs leading to study drug discontinuation occurred during this study. There were 2 clinically significant AEs of thrombocytopenia (1 mild and 1 moderate), which were considered to be unrelated to the study drug. One subject had a clinically significant AE of moderate orthostatic hypotension that was considered to be possibly related to the study drug. One subject experienced a moderate ECG PR prolongation that was considered to be possibly related to the study drug.

In the divalproex study to assess the effect of a multiple-dose regimen of cenobamate on the plasma PK of divalproex, no significant drug interactions between cenobamate and divalproex were noted. Ten of the 16 subjects experienced a total of 44 AEs; of these, 33 were mild, 10 were moderate, and there were no severe AEs. The most commonly reported AEs were somnolence (n=10) and nausea (n=6). No deaths, SAEs, or AEs leading to study drug discontinuation occurred during this study.

In the phenytoin interaction study assessing co-administration of cenobamate with phenytoin, with an observed resulting in increases in phenytoin exposure and decreases in cenobamate systemic exposure. Fifteen of the 16 subjects experienced a total of 187 AEs; of these, 159 were mild, 26 were moderate, and 2 were severe AEs (nausea and increased anticonvulsant drug concentration). The most commonly reported AEs were increased GGT (69%), headache (56%), ataxia (50%), somnolence (38%), dizziness (38%), nausea (38%), increased ALT (31%), and increased anticonvulsant drug level

(31%). There were no deaths in this study. One subject experienced an SAE of antiepileptic hypersensitivity syndrome, which was considered drug related, and withdrew from the study due to this AE.

Data from phenobarbital interaction study showed a significant effect of cenobamate on the disposition of phenobarbital (+34% for Cmax,ss and +37% for AUC0-τ). Thirteen of the 16 subjects experienced a total of 96 AEs; of these, 75 were mild, 21 were moderate, and none were severe AEs. The most commonly reported AEs were weight decreased (8 [50%] subjects), followed by nausea, headache, and dizziness (4 [25%] subjects each). There were no deaths or SAEs reported in this study. Two subjects experienced drug-related rash events (angioedema and erythematous maculopapular rash); both events were moderate in intensity and considered to be related to both cenobamate and phenobarbital. One of the subjects discontinued from the study due to the event.

The DB Pool comprised 76 patients receiving 1 concomitant ASM, 185 patients receiving 2 ASMs, and 181 patients receiving more than 2 ASMs in the cenobamate group; and 28 patients receiving 1 concomitant ASM, 98 patients receiving 2 ASMs, and 90 patients receiving more than 2 ASMs in the placebo group. The median duration of exposure to cenobamate was higher than for placebo for patients treated with 2 ASMs (17.86 weeks with cenobamate, 13.21 weeks for placebo), and more than 2 ASMs (18.00 weeks with cenobamate, 14.50 weeks for placebo). For patients receiving ≥2 ASMs the proportion of patients treated for ≥12 weeks was lower for the cenobamate group (84.0% vs. 93.3% placebo).

The overall frequency of AEs was higher for patients treated with cenobamate compared with placebo patients treated with >2 ASMs; a dose-related increase in the overall event frequency was also seen for patients treated with 2 or >2 other ASMs. There was no notable difference in the overall AE rate when comparing groups taking different numbers of concomitant ASMs. Cenobamate-treated patients taking >2 concomitant ASMs had a higher overall frequency of treatment-related AEs than those taking 2 ASMs and higher proportions of patients also having dizziness (30.4% vs. 14.6% of those taking 2 ASMs) and somnolence (29.8% vs. 18.9%).

Higher study discontinuation was described in patients having a higher number of concomitant ASMs.

In study C021, patients were given cenobamate on top of different monotherapy with phenytoin (N=83), phenobarbital (N=37) and other non-specified ASMs (N=1220)). The proportion of AEs were slightly higher for patients receiving cenobamate with phenobarbital, namely with somnolence and fatigue. The frequency of toxicity to other agents was higher for patients receiving cenobamate and phenytoin. The frequency of other AEs was comparable between treatment groups. AEs severity, Treatment-related AEs, Severe AEs proportion and rate of study drug discontinuation due to AEs were comparable among groups.

Analyses of several subgroups of concomitant ASMs were undertaken:

- Safety and efficacy analyses of GABA modulators and sodium channel blockers were undertaken because of a focally overlapping mechanism of action with cenobamate. Overall, there were no notable differences in the frequency of severe, treatment-related or serious AEs or AEs leading to discontinuation when comparing patients who did or did not use concomitant sodium channel blockers or GABA modulators.

- Given the specificity of the $GABA_A$ receptor and the safety profile of benzodiazepines which differ from other GABA-ergic ASMs, benzodiazepines were analysed separately from the other GABA modulators (and not included in the GABA modulator analysis). An increase in AE rates, notably somnolence was observed, but no additional safety signals were detected. However, it should be noted that the population of patients on benzodiazepines was small.

- A further safety analysis was done for the subpopulation of patients on concomitant clobazam, which was the most frequently prescribed benzodiazepine. Note, the population of patients on clobazam was also included in the full benzodiazepine analysis. Cenobamate has the potential to increase levels of the clobazam active metabolite via induction of CYP3A and inhibition of CYP2C19. A subanalysis of patients in Study C017 showed an increased frequency of certain adverse events, including dizziness, somnolence, and fatigue in patients taking clobazam compared to those not taking clobazam.

In the study on co-administration of cenobamate with the oral contraceptive Ortho-Novum for 14 days, a total of 23 (82.1%) subjects reported 152 AEs during the study. The greatest number of AEs was reported following dosing with combination therapy (79 AEs in 18 [64.3%] subjects), followed by cenobamate monotherapy (55 AEs in 18 [69.2%] subjects), and Ortho- Novum monotherapy (18 AEs in 12 [42.9%] subjects). The majority of AEs were mild (138 of 152 AEs). There were no deaths or SAEs were reported.

Discontinuation due to adverse events

In the DB pool a larger proportion of patients receiving cenobamate experienced an AE that led to study drug discontinuation (13.1% vs. 4.2% in the placebo group). The most frequent AEs that led to study drug discontinuation were ataxia, dizziness, somnolence, vertigo, and nystagmus. The incidence of study drug discontinuation due to an AE slightly increased with dose for most preferred terms.

In the Phase 2/3 Pool, AEs leading to treatment discontinuation occurred in 14.3% of the patients. The only AE leading to discontinuation in >1% of patients was dizziness (29 patients, 1.5%).

AEs leading to treatment discontinuation (19.0% vs. 13.1%) were higher in the LT OLE Pool than for the DB Pool. AEs leading to treatment discontinuation were slightly lower in Study C021 compared to the DB Pool (10.2% vs. 13.1%)

The proportion of patients taking cenobamate who had AEs leading to treatment discontinuation was higher for patients receiving 2 concomitant ASMs (11.4% of those receiving cenobamate vs. 5.1% of those receiving placebo; 7.0% for the 100 mg/day dose group, 8.2% for the 200 mg/day group and 22.7% for the 400 mg/day group) and for patients receiving >2 ASMs (14.9% of those receiving cenobamate vs. 2.2% of those receiving placebo.

The proportion of patients with AEs leading to treatment discontinuation was comparable for cenobamate-treated patients using concomitant sodium channel blockers (13.1% for cenobamate-treated patients vs. 3.9% for the placebo group) and those not using sodium channel blockers (13.1% vs. 5.3%).

The proportion of patients with AEs leading to treatment discontinuation was similar for cenobamate-treated patients using concomitant GABA modulators (13.2% vs. 4.8% for the placebo group) and those not using GABA modulators (13.1% vs. 3.6%).

The proportion of patients with AEs leading to treatment discontinuation was higher for cenobamate-treated patients using concomitant benzodiazepines (17.1% vs. 7.5% for the placebo group) than those not using benzodiazepines (11.8% vs. 3.1%; 8.5% for the 100 mg/day dose group, 9.5% for the 200 mg/day group and 20.0% for the 400 mg/day group).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

Overall, the safety profile of cenobamate has been well characterised through the clinical development programme with high completion rates in the DB Pooled population, and high retention and long exposures in both the LT OLE studies, and in the large open label safety study C021. The profile of AEs in cenobamate-treated patients was consistent between studies and analysis pools when considering a range of common treatment-related AEs, primarily somnolence, dizziness, fatigue and headache.

The most common adverse events reported were somnolence, dizziness, fatigue and headache. Other common events included confusional state, irritability, diplopia, dysarthria, nystagmus, aphasia and memory impairment. Other AEs seen at lower frequency included ataxia and gastrointestinal events such as nausea, vomiting and constipation

The vast majority of the AEs were mild to moderate in nature and resolved with the time.

The exposure-adjusted event rate showed a dose relationship for dizziness, somnolence, fatigue, nausea, balance disorder, nystagmus, constipation, vomiting, gait disturbance, ataxia, dysarthria, vertigo, confusional state, blurred vision and ALT increase.

AEs leading to discontinuation were higher for cenobamate compared to placebo in the DB Pool and highest in the 400 mg/day group.

Different **titration schemes** were used in the clinical studies. Generally, frequency and pattern of AEs were similar across titration schedules, however the severity was higher with the faster weekly titration schemes. In particular, all 3 DRESS cases occurred in studies with rapid titration. Even though the proposed gradual slower titration scheme (every 2 weeks) was only assessed in a safety targeting trial (C021), the CHMP agreed that it is supported by the safety results and would mitigate more common AEs.

There was a decrease in frequency of AEs during the **maintenance compared to the titration phase** for all patients treated with cenobamate and the placebo group. Somnolence, dizziness and fatigue frequency across the dose groups was notably lower during the maintenance phase than during the titration phase. It was comparable to the frequency seen in the placebo group, even in the 400 mg/day arm.

No new safety signals were seen in the long-term data. With long term exposure, AEs were similar in nature to those seen in the DB studies. There was a slight increase in the frequency of AEs likely due to the longer treatment duration.

Adverse events of special interest included events of suicidal nature, selected adverse skin reactions and DRESS.

Cenobamate did not appear to result in increases in **suicidal ideation, intensity or behaviour** above the expected background rate. Even though some cases of completed suicide and suicidal behaviour/suicidal ideation were described, after reviewing the cases, the CHMP agrees that most suicidality cases resolved without treatment reduction or discontinuation and that the warning in SmPC section 4.4 regarding the risk of suicidal ideation is acceptable.

Proportions of patients experiencing **skin reactions** and those leading to discontinuation were comparable for patients receiving cenobamate and placebo. There were no Grade 5 skin reactions and

no reports of Stevens-Johnson syndrome and toxic epidermal necrolysis. DRESS was reported in 3 patients, all in studies with rapid (weekly) titration scheduled.

QT shortening was observed in the clinical programme and a dose-dependent shortening of the QTcF interval has been observed with cenobamate (see pharmacology discussion). This important safety concern could not be fully clarified, as, for instances, it was unclear whether cardiovascular compromised individuals were included in the studies. The incidence of subjects with cardiac disorder TEAEs across the cenobamate and placebo groups was comparable. Pre-clinical data did not support an increased cardiovascular risk. Of the subjects with cardiac past medical history the majority were able to complete the double-blind studies and remain in the study at the time of data cut-off (82.9%). In long term open label studies, 3 cases of cardiovascular AEs with an outcome of death occurred in subjects taking cenobamate for at least 1 year and 11 months. Additionally, cardiac disorder SAEs occurred in 2 elderly subjects in long term open label studies after at least 6 months of treatment. Sinus bradycardia and supraventricular tachycardia, atrioventricular block complete and atrioventricular block first degree were the only events that were reported in patients >65years old. There is insufficient information on these cases to assess any contribution of cenobamate or other ASM. Overall, in view of the available data, the CHMP agrees to inclusion of a warning in the SmPC regarding caution when prescribing cenobamate in combination with other medicinal product known to shorten the QT as well as the contraindication for use in patients with "Familial short QT syndrome".

There were 2 reports of hyperkalaemia in the clinical programme no critical values were identified and none were associated with cardiac AEs. The CHMP therefore agrees no further action is needed.

There seems to be a trend for decreased platelet levels with cenobamate treatment both in the DB and LT OLE groups assessment but with no impact on the percentage of subjects with shifts from normal at baseline to low during treatment.

There were no intentional cases of cenobamate overdose, misuse, abuse, diversion or dependence. There were very few discontinuation-emergent AEs reported that could be interpreted as withdrawal or rebound effects. Data did not point to a higher incidence of mood effects, including euphoria.

In view of the notable difference in the frequency of the AEs related to the ability to drive or operate a machinery between the cenobamate and placebo group, the CHMP agrees with the recommendation not to drive or operate a machinery while treated with cenobamate.

The overall incidence of subjects with TEAEs for the renal impairment subgroup for cenobamate treated subjects did not differ from those with normal creatinine clearance. Similarly, the overall incidence of cenobamate subjects with TEAEs for the elevated transaminase subgroup did not differ from those with normal transaminase levels.

Whereas the available data showed no additional safety risk in elderly subjects, a higher incidence of adverse events such as fatigue, gait disturbance, fall, ataxia, balance disorder, dizziness and somnolence was observed in subjects above 65 years of age. The CHMP agrees with the proposed SmPC wording regarding the use in patients > 65years old in section 4.2 and 4.8 of the SmPC.

Analyses of several subgroups of concomitant ASMs were also undertaken and demonstrated no notable differences in the frequency of severe, treatment-related or serious AEs or AEs leading to discontinuation when comparing patients who did or did not use concomitant sodium channel blockers or GABA modulators. Cenobamate-treated patients using concomitant benzodiazepines had an increase in AE rates, notably somnolence, and had a higher proportion of AEs leading to treatment discontinuation. It was however noted that the population of patients on benzodiazepines was small. A further safety analysis was done for the subpopulation of patients on concomitant clobazam, the most frequently prescribed benzodiazepine, and the 400mg cenobamate dose was associated with more AEs

especially when taken concomitantly with clobazam, suggesting a need to decrease clobazam. The information is correctly reflected in section 4.4 and 4.8 of the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The CHMP agrees that the available safety data are sufficient to allow a benefit-risk assessment in claimed indication.

2.7. Risk Management Plan

Safety concerns

Summary of the safety concerns

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

Pharmacovigilance plan

Table 27: Table of Ongoing and planned additional pharmacovigilance activities in the PV Plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Inclusion of cenobamate in EURAP - An International Registry of Antiepileptic Drugs and Pregnancy Planned **Category 3**	EURAP's primary goal is to compare the risk of major congenital malformations following maternal intake of different ASMs, incl. cenobamate 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	Novembe r 2020
			EURAP publishes semi-annual reports of the progress of the project twice a year that are publicly available	May and Novembe r each year

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Any findings of significance related to cenobamate will be reported in the PSURs	PSUR reports

Risk minimisation measures

Table 28: 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 systemic symptoms (DRESS)	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for DRESS **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: 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.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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. Legal status: medical prescription **Additional risk minimisation measures:** None	None
Important potential risk 3: 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 Legal status: medical prescription **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up questionnaire for cardiac arrhythmia **Additional pharmacovigilance activities:** None
Important potential risk 4: 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EURAP - An International Registry of Antiepileptic Drugs and Pregnancy

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	

Conclusion

The CHMP and PRAC considered that the RMP version 1.0 is acceptable.

With regards to future post-marketing exposure estimations (i.e. also in PSURs), the applicant should continue to consider the Defined Daily Dose (DDD) for cenobamate, as established by the WHO Collaborating Centre (200 mg), and, in particular, detail how the titration period and maintenance period are, respectively, taken into account in this calculation.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.11.2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of cenobamate with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers cenobamate to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ontozry (cenobamate) is included in the

additional monitoring list as cenobamate is a new active substance and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

The aim of the treatment is to significantly reduce seizure frequency and eliminate them if possible, while not adding drug-related morbidity.

3.1.2. Available therapies and unmet medical need

Antiepileptic Drugs (ASMs) are the mainstay of epilepsy treatment, but adverse events of ASMs are a major source of disability, morbidity, and mortality. Adverse effects result in early treatment discontinuation in up to 25% of patients. Cutaneous manifestations of hypersensitivity are the most common idiosyncratic reactions to ASMs and range from mild urticarioid/maculopapular eruptions to the more severe drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Approximately 63% of people with epilepsy will achieve longer-term seizure freedom, and most achieve that after the first or second ASM treatment. However, approximately 35 to 40 % of epilepsy cases, particularly those with focal seizures are drug resistant. When a first ASM fails, further ASMs will be initiated. 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. Chen *et al* demonstrated that the initial ASM leads to 45.7% of patients achieving seizure freedom. If the initial ASM is ineffective, the second ASM results in an 11.6% chance of seizure freedom. Once a patient has failed a second ASM only 4.4% will achieve seizure freedom if a third regimen is required. For patients who failed 3 ASMs, only 2.1% of patients will achieved seizure control on multiple subsequent ASM regimens irrespective of the specific medications chosen. Some studies suggest that compared to all patients with epilepsy, those with focal onset epilepsy have an even higher risk of >50% to develop Drug Resistant Epilepsy (DRE).

3.1.3. Main clinical studies

The main evidence of efficacy is a phase II multicentre, randomised, double-blind comparing cenobamate in three different doses (n=329) versus placebo (n=108) as adjunctive treatment for patients with Focal-Onset Seizures who have failed at least two previous treatments with 12 weeks maintenance period (study C017).

A second phase II multicentre randomised, double-blind comparing cenobamate 200 mg vs placebo as adjunctive in on treatment for patients with Focal Onset Seizures who have failed at least two previous treatments and 6 weeks maintenance period (study C013) supports the main study.

3.2. Favourable effects

The data from the main and supportive studies confirmed the efficacy of Ontozry in the claimed indication:

Study C017:

- The responder rate (as primary endpoint: responder as at least 50% Focal Onset Seizure frequency reduction) was 40.2% for 100mg cenobamate, 56.1% for 200mg cenobamate and 64.2% for 400mg cenobamate as compared to 25.5% for placebo.

- The % change in seizure frequency FOS frequency rate (secondary endpoint) in the maintenance phase (median, minimum, maximum) was -41.5; -100, 150 for 100mg, -56.5; -100, 188 for 200mg and -63.0; -100, 133 for 300mg compared to -27.0; -100, 282 for placebo.

- 3.9% of 100mg subjects were seizure free during the maintenance phase (secondary endpoint: responder as 100% FOS frequency reduction), 11.2% for 200mg and 21.1% for 400mg compared to 1.0% for placebo.

- Regarding the responder rate for (≥50% seizure frequency reduction) FOS frequency reduction in secondarily generalised, focal to bilateral tonic-clonic seizures during the maintenance phase (secondary endpoint), there was 61.8% responders in the 100mg group, 78.1% for 200mg and 66.7% for 400mg compared to 48.8% for placebo.

Study C013 yielded comparable results for cenobamate 200 mg vs. placebo, based upon original statistical analysis plan.

3.3. Uncertainties and limitations about favourable effects

The main limitations regarding the main C017 study results (and the supportive study C013) is the methodology for assessment of responders. It is based upon a seizure diary, and missing data in the diary is counted as the mean value within the studied period. Also, drop-out patient data missingness would also be similarly treated. To reduce the uncertainty and confirm the result robustness, supplementary analyses with different estimand and sensitivity analysis with different imputation strategies have been conducted. The analyses provided have confirmed the magnitude of results and increased robustness.

Sub analyses show that patients on treatment with lamotrigine and benzodiazepines) have less improvement. For Lamotrigine, this is believed to be due to a PK interaction with cenobamate perpetrating over lamotrigine and is described in the SmPC. For benzodiazepine, this is probably due to baseline imbalances in the trials.

Although focal onset seizures are the most common seizure in elderly patients, scarce data is available regarding patients older than 65 years of age.

Although the open-label extension studies have durations of up to 5 years, in view of the high placebo effect, the magnitude of cenobamate effect on the long term cannot be ascertained. No randomised withdrawal study has been performed.

3.4. Unfavourable effects

The following unfavourable effects were identified:

- Drug reaction with eosinophilia and systemic symptoms (DRESS):

    - Considered as an adverse event of special interest, DRESS was described in 3 subjects of the clinical trials (1 patient with epilepsy and 2 healthy volunteers). One patient died with eosinophilic myocarditis that was associated with DRESS and considered possibly related to cenobamate. DRESS occurred in subjects in studies starting at higher doses (>= 50mg) and with rapid (weekly or less) titration scheduled. Study C021 was conducted with a slower titration scheme (as proposed in the SmPC) and no new cases of DRESS have been described in more than 1340 patients exposed (including 1134 patients for at least 6 months).

    - The risk for higher than expected starting dose and DRESS development exists.

- Somnolence, Dizziness, Vertigo, Balance disorder, Ataxia, Gait disturbance and abnormal coordination, Headache:

    - These ADRs are more frequently described for all doses, titration schemes and ASMs combinations, with dose-relationship documented for some of them. They were mostly mild to moderate and seldom associated with study drug or study withdrawal.

    - Ataxia and dizziness were the most frequent AEs leading to treatment discontinuation.

- Dysarthria, Nystagmus, Aphasia, Memory impairment, Confusional state, Irritability: these ADRs were described by some patients and may be a diagnostic challenge due to the patient' background condition or co-treatments.

3.5. Uncertainties and limitations about unfavourable effects

The following uncertainties regarding the unfavourable effects were identified:

- Potential for higher rate of AEs depending on the combinations with other ASMs or other drugs:

    - Not enough evidence has been generated on the possible different drug combinations to be sure on what are the safer and more AEs associated combination treatments.

- Interaction with Oral Contraceptives:

    - No formal studies have been conducted to assess Contraceptive Use impact of cenobamate at doses higher than 100mg doses which are expected to be taken.

- QT shortening:

    - Although QT shortening had no clinically significant impact at proposed treatment doses there was a significant decrease of QTcF of unknown clinical relevance at higher doses. The cardiac risk in cases of overdose is possible. No information on exposure of patients with established cardiovascular disease is discussed.

- Information on exposure in renal or hepatic impaired patients on the clinical studies is lacking.

- There is a lack of information on exposure of patients older than 65years old.

3.6. Effects Table

Table 29: Effects Table for Cenobamate for the adjunctive treatment of focal-onset seizures

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
50% FOS Responders rates maintenance	⩾50% Focal Onset Seizure (FOS) Responder Rate Maintenance period	%	100 mg: 40.2 200 mg: 56.1 400 mg: 64.2	PLO: 25.5	Drop-out rate + missing data in seizure diaries decrease robustness of results	Study C017
% change in seizure FOS frequency Maintenance	% change in FOS frequency rate, Maintenance Phase (Median)	Median	100 mg: -41.5 200 mg: -56.5 400 mg: -63.0	PLO: -27.	Drop-out rate + missing data in seizure diaries decrease robustness of results	Study C017
Seizure free during maintenance	100% FOS Responder Rate Maintenance Phase	%	100 mg: 3.9 200 mg: 11.2 400 mg: 21.1	PLO: 1.0	Drop-out rate + missing data in seizure diaries decrease robustness of results	Study C017
50% FOS Responder Rate (Type D) Maintenance Phase	⩾50% FOS Responder Rate secondary generalised seizures Maintenance Phase	%	100 mg: 61.8 200 mg: 78.1 400 mg: 66.7	PLO: 48.8	Drop-out rate + missing data in seizure diaries decrease robustness of results	Study C017
Unfavourable Effects						
DRESS	AE of special interest that was described in 3 subjects (1 patient with epilepsy and 2 healthy volunteers) 1 patient died		Titration rate related		Risk for occurrence if faster titration rate	Safety data pool
Somnolence, Dizziness, Vertigo, Balance disorder, Ataxia, Gait disturbance and abnormal coordination, Headache	The more frequently described adverse reactions, transversal to all doses, titration schemes and ASMs combinations		dose relationship having been documented for some of these ADRs			Safety data pool

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Dysarthria, Nystagmus, Aphasia, Memory impairment, Confusional state, Irritability	may be a diagnostic challenge due to the patient's background condition or co-treatments					Safety data pool
Potential for higher rate of AEs depending on the combinations with other ASMs or other drugs	Cenobamate-treated patients use with concomitant benzodiazepines had higher discontinuation rates. Combination of more ASMs was associated with higher rate of AEs.				Not enough evidence has been generated on the possible different drug combinations to be sure on what are the safer and more AEs associated combination treatments	Safety data pool
Interaction with Oral Contraceptives	Available data resulted in a recommendation to consider the use a non-hormonal contraceptive measure when taking cenobamate				No formal studies have been conducted to assess Contraceptive Use impact of cenobamate at dose higher than 100mg doses which are expected to be taken.	Safety data pool
QT shortening	QT shortening was observed in the clinical programme.				Although this sign had no clinically significant impact at proposed treatment doses there was a significant decrease of QTcF (of unknown clinical relevance) at higher doses. Risk of development in cases of overdose is possible.	Safety data pool

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoints were met in both Phase II clinical studies. Statistically significant difference in responder rate for each of the cenobamate treatment groups compared to placebo during the

maintenance phase was demonstrated in Study C017. The percent change in seizure frequency per 28 days was statistically significant higher in cenobamate 200 mg group ($p<0.0001$) compared to placebo group in Study C013.

The magnitude of effect on the reduction of seizure frequency is clinically significant, particularly in relation to the studied population which tends to become treatment resistant. An improvement of 20 to 40% over placebo is deemed significant.

Besides DRESS which is a concern and must be actively monitored, most adverse events are CNS related. The safety profile with the frequency of somnolence, fatigue and dizziness is of concern, especially in the highest cenobamate group. Dizziness, leading to discontinuation, should also be managed and minimised.

Drug-drug interactions, particularly with cenobamate as perpetrator is of concern, both for other ASMs and contraceptives. QT shortening has not raised as a concern within therapeutic range, but it may cause significant AEs in the higher doses.

3.7.2. Balance of benefits and risks

The benefit of cenobamate in an adjunctive treatment of focal onset seizure in adult who have not been adequately controlled despite treatment with at least 2 anti-epileptic medicinal products has been appropriately demonstrated. The effects on seizures frequency are clinically relevant and the overall benefit outweighs the unfavourable effects.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ontozry is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ontozry is not similar to Epidyolex or Fintepla within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ontozry is favourable in the following indication:

Ontozry 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cenobamate is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.