

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212839Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	212839
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Submit Date(s)	11/21/2018
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Division/Office	DN2/ Office of Neuroscience
Reviewer Name(s)	Steven Dinsmore, DO
Review Completion Date	10/15/19
Established/Proper Name	YKP3089
(Proposed) Trade Name	XCOPRI
Applicant	SK Life Science, Inc.
Dosage Form(s)	Tablet 12.5mg, 25mg, 50mg, 100mg, 150mg, 200mg
Applicant Proposed Dosing Regimen(s)	initial dose of XCOPRI is 12.5 mg once daily for two weeks; followed by 25 mg once daily for two weeks; followed by 50 mg once daily for two weeks. Increase the dose in bi-weekly increments by no more than 50 mg once daily to a recommended maintenance dose of (b) (4) mg once daily. Maximum daily dose is 400 mg
Applicant Proposed Indication(s)/Population(s)	indicated for the treatment of partial-onset seizures in adult patients.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	XCOPRI is indicated for the treatment of partial-onset seizures in adult patients.

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Glossary

AC	advisory committee
AE	adverse event
AED	Antiepilepsy drug
AEOUT	Adverse Event Outcome variable.
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIS	Clinical Inspection Summary
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Event (National Cancer Institute)
DILI	drug induced liver injury
DMC	data monitoring committee
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
eCTD	electronic common technical document
EOT	End of treatment
ETASU	elements to assure safe use
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
INN	International Nonproprietary Name

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OL	open label
OORR	out of reference range
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	Postmarketing commitment
PMR	Postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System organ class of MedDRA hierarchy
SUDEP	sudden unexpected death in epilepsy
TEAE	treatment emergent adverse event
TQT	thorough QT study
YKP	study drug name during development, YKP3089, cenobamate

1. Executive Summary

1.1. Product Introduction

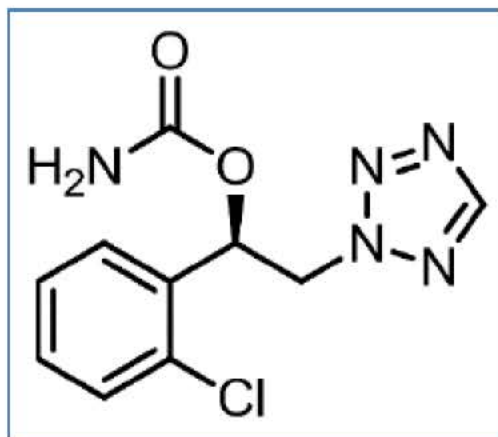
Cenobamate is a novel tetrazole derived compound with one chiral center.

Chemical Name: [(1R)-1-(2-Chlorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate

Molecular Formula: C₁₀H₁₀ClN₅O₂

Molecular weight is 267.67 g/mol.

Figure 1 Cenobamate structure¹



Cenobamate drug substance was originally discovered by SK Biopharmaceuticals Co., Ltd. and was given a laboratory code, YKP3089. The name cenobamate was adopted as an INN and both terms are used interchangeably throughout the New Drug Application (NDA). Cenobamate has been shown to reduce repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of 6 subtypes of the γ -aminobutyric acid ion channel.

Proposed Indication: Cenobamate is indicated for the treatment of partial-onset seizures in adult patients.

Proposed Dosing: The recommended initial dose of XCOPRI is 12.5 mg once daily for two weeks; followed by 25 mg once daily for two weeks; followed by 50 mg once daily for two weeks. Increase the dose in bi-weekly increments by no more than 50 mg once daily to a recommended maintenance dose of (b) (4) mg once daily. Maximum daily dose is 400 mg.

¹ eCTD Module 2.2 Introduction

Recommended Indication: treatment of partial-onset seizures in adult patients

Recommended Dosing Information: The recommended initial dosage of XCOPRI is 12.5 mg once daily for two weeks; followed by 25 mg once daily for two weeks; followed by 50 mg once daily for two weeks. Increase the dose in bi-weekly increments by no more than 50 mg once daily to a recommended maintenance dose of 200mg once daily. Based on individual patient response and tolerability escalation to a maximum daily dosage of 400 mg may provide additional benefit.

A table of the dose regimen will also be included in the label to assist interpretation of the narrative titration schedule.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The studies included in the NDA submission for cenobamate contain two adequate and well controlled clinical trials that meet the evidentiary standard for effectiveness. Both studies were double-blind, randomized, placebo-controlled, parallel group multicenter, multinational studies. These were studies C013 and C017.

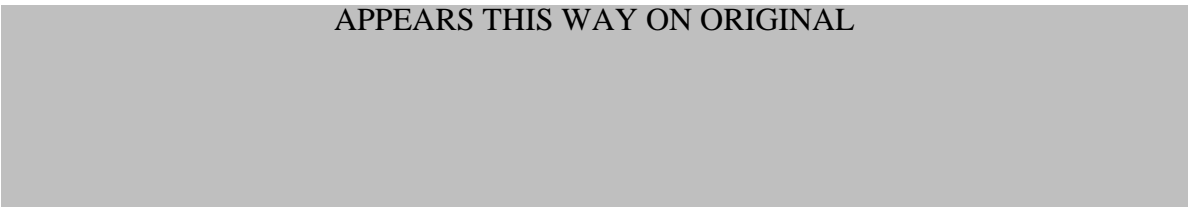
Study C013 was a two-arm study with 109 patients treated with placebo and 113 patients in the 200mg cenobamate treatment arm. There was significant separation between placebo and treatment with a 28-day median percent seizure reduction from baseline to treatment of 56% with an effect size of 34%. The p-value for comparing the medians of the two treatment groups was nominally smaller than 0.05.

Study C017 was a 4-arm, multi-center, Phase 2 clinical study to determine the effective dose range of cenobamate as adjunctive therapy for the treatment of partial seizures. The study also aimed to evaluate the safety and tolerability of cenobamate in the partial epilepsy population. Approximately 400 subjects aged 18- 70 years (inclusive) were planned to be enrolled and randomized in a 1:1:1:1 ratio to receive cenobamate 400 mg once daily, cenobamate 200 mg once daily, cenobamate 100 mg once daily, or placebo. There were 106, 108, 109, and 111 patients in the placebo, 100mg, 200mg, and 400mg arms respectively. The observed medians of percent change from baseline in seizure frequency per 28 days were -55.3%, -55.2%, -36.3%, and -24.3% for the cenobamate 400 mg/day group, cenobamate 200 mg/day group, cenobamate 100 mg/day group, and placebo group, respectively. All three cenobamate dose groups were statistically significantly different from the placebo based on the rank ANCOVA model.

The reviewer from Division of Biometrics 1 concludes that collective evidence from Study C013 and Study C017 indicates that YKP3089 is effective for the treatment of partial onset seizures in adult patients.

1.3. **Benefit-Risk Assessment**

APPEARS THIS WAY ON ORIGINAL



Benefit-Risk Integrated Assessment

Epilepsy is a common condition that affects 1% of people worldwide where partial onset seizures (focal) are the most common subset. These seizures are a threat to the patient on any occurrence where loss of consciousness occurs. In some circumstances such an event may be fatal. High frequencies of seizure are also associated with an increased risk of sudden unexpected death in epilepsy (SUDEP). Frequent partial seizures may promote a propensity for progression of the seizure disorder through kindling. When an outcome is not a threat to life, all events are disruptive to quality of life. The proposed indication for cenobamate, partial onset seizures (focal), is directed at a population of patients where a medical need remains.

There have been multiple antiepilepsy drugs added to the armamentarium for epilepsy treatment in the past 25 years. Despite these additions, approximately 30% of patients remain refractory to treatment. Although the number of available antiepileptic drug (AED) therapies has expanded, in clinical practice, patients who fail one AED are given a trial of an alternate drug to assess benefit. This is an ongoing process and it is unpredictable, on an individual basis who will benefit from a particular agent. There is a continuing need for more alternative AEDs.

In this submission, two pivotal studies identified a reproducible robust separation of treatment from placebo. The endpoint of median percent change from baseline to treatment per 28 days revealed a -55.6 percent reduction from baseline at the 200mg dose in study C013. The percent change from baseline in study C017 treatment arms were -24.3, -33.6, -55.2 and -55.3 in the placebo, 100mg, 200mg and 400mg arms respectively. The dose response appears flat after 200mg but the 50% responder rate shows additional benefit of the 400mg treatment arm over the 200mg treatment arm. Neurologic adverse events were dose proportional. A dose of 200mg will be the recommended maintenance dose with escalation to a maximum dose of 400mg based on individual patient response and tolerability.

The primary risk identified in cenobamate treatment was Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). See Section 8.6.1., [DRESS Risk](#). A DRESS case occurred in the TQT (thorough QT) healthy volunteer study that had a fatal outcome. Two additional cases of DRESS occurred, one in a healthy volunteer participating in a PK multiple ascending dose study and one in a patient participating in the open label extension of study C017. These latter two patients recovered but did require hospitalization and corticosteroid treatment. DRESS risk may be associated with the rate of dose escalation. A long-term open label safety study in epilepsy patients, study C021, initiated treatment with a reduced rate of dose escalation. No cases of DRESS were identified among 1339 subjects treated with YKP3089, including 1110 subjects treated with YKP3089 for at least 6 months where a lower starting dose (12.5 mg/day) and a slower titration rate (every 2 weeks) was used. This study sample size was chosen, such that with no new cases of DRESS, it would establish a 0.3% upper limit of the 95% confidence interval for the rate of DRESS with the modified titration rate. This conclusion has a favorable bias because the reduced titration rate was not tested in a

randomized controlled trial and there are underlying differences between the population in study C021 and the populations from which the DRESS cases were identified. However, the study offers assurance that DRESS risk may be managed in the intended treatment population, with a reduced titration rate and vigilance for features of a hypersensitivity reaction.

Additional risks identified were QTc shortening and neurologic adverse events as well as possible associations with hyperkalemia and appendicitis. This represents an uncertain threat. This threatening cardiac dysrhythmia was first identified in individuals with familial short QTc syndrome. Cenobamate will be contraindicated in these patients and drugs that are known to reduce QTc interval should be used with caution. This will be delineated in the label. Neurologic adverse events had a high frequency with cenobamate treatment. These adverse events are frequent in AED therapy. These may be monitored, will resolve with discontinuation and generally diminish with accommodation to the drug treatment. A trend of hyperkalemia was identified and will be included in labeling to alert prescribers, but no critical values were identified that were associated with adverse cardiac adverse events. The events of potassium elevated out of reference range to high value tended to be sporadic. This sporadic occurrence leads to uncertainty about causal association. Clinical chemistry monitoring will not be indicated. An adverse event of appendicitis, occurring at a rate higher than the background rate was identified in long term use of cenobamate. The causal relationship is unclear. This event will be added to the label to inform prescribers of the observation.

The high-risk adverse event of DRESS may be managed by a slow dose escalation and informing patients of hypersensitivity features that require professional assessment. Although this is a threatening adverse event, it is also seen in a broad array of approved drug treatments across a variety of disease states, see Section 8.6.1 [DRESS risk](#). The potential benefit of a new AED provides practitioners in the epilepsy community an additional option for treatment of this serious medical illness. The risk of DRESS, QTc shortening and neurologic adverse events are not disproportionate to the potential benefit in the patient population with this treatment indication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 30% of patients with epilepsy remain refractory to current available AED therapy • Epilepsy is a life shortening disease of the brain. It may episodically be life-threatening. • The disease process (epileptogenesis) may also lead to the progression of epilepsy after the onset of seizures.	Effective therapy may reduce threat to life and epilepsy progression as well as associated comorbidities.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Epilepsy is associated with substantial comorbidity, including depression, anxiety and increased mortality	
Current Treatment Options	There are 17 available therapies, 30% of patients with partial onset seizures remain refractory.	Although there are 17 available AEDs for partial onset seizures, in clinical practice patients who fail one AED will be given a trial of an alternate drug to assess benefit. This is an ongoing process and it is unpredictable on an individual basis who will benefit from a particular agent. There is a continuing need for available alternatives
Benefit	Cenobamate has a favorable effects size at the upper end of effect size seen in products for the treatment of partial onset seizures.	There is potential for response in currently refractory patients in the partial onset seizure, epilepsy population.
Risk and Risk Management	- DRESS - Neurological adverse effects - QTc Shortening - Appendicitis - hyperkalemia	Hypersensitivity and DRESS. 3 cases of DRESS, one fatality. In study C021 DRESS risk was addressed by reduced titration rate and pharmacovigilance. Study C021 did not reveal further instances of DRESS. Reduced titration rate in labeling will be the same as in study C021. A Medication Guide will be implemented to alert patients to features of DRESS syndrome and direct to appropriate action. There are also prominent early cenobamate intolerance due to CNS adverse effects

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		including somnolence and dizziness. These CNS adverse effects tended to abate as treatment was maintained. These adverse reactions may be monitored, and, if necessary, cenobamate may be discontinued QTc Shortening presents an uncertain risk in the general population. Labeling will contraindicate patients with known QTc shortening syndrome and also caution against use with other medications that shorten the QT interval. Appendicitis was observed at a higher rate than typical background frequency in the open label long term data. This will be presented in the labeling, although causal relationship to cenobamate is uncertain. A shift to increased post baseline potassium values was observed. There were no critical outlier values in controlled study data. Labeling will contain an entry in “laboratory abnormalities” to alert practitioners to this observation.

2. Therapeutic Context

2.1. Analysis of Condition

Epilepsy is a life shortening disease of the brain. It may episodically be life threatening. This disorder affects approximately 1% of the worldwide population. Although repeated epileptic seizures are the clinical hallmark of epilepsy, the disease process (epileptogenesis) begins before the first seizure and may also lead to the progression of epilepsy after the onset of seizures. Epilepsy is diverse, with over 15 different seizure types and over 30 epilepsy syndromes, and it is associated with substantial comorbidity, including depression, anxiety and increased mortality. Approximately 70 to 80% of patients with new onset epilepsy may enter remission with current AEDs, However, 20 to 30% of patients remain refractory to available therapy.

2.2. Analysis of Current Treatment Options

Analysis of Current Treatment Options

Table 1 Summary of drugs currently approved for treatment of partial onset seizures²

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Brivaracetam (BRV)	Treatment of partial-onset seizures in patients 4 years of age and older	2018	PO/IV, BID Weight-based dosing pediatric pts	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: Neurological Adverse Reactions (somnolence and fatigue, dizziness and disturbance in gait and coordination), Psychiatric Adverse Reactions (including aggression, anger, agitation, depression, hallucination, paranoia, acute psychosis, and psychotic behavior), bronchospasm and angioedema.
Eslicarbazepine (ESL)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO, QD Weight-based dosing ages 4-17 yrs	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Pediatric safety data not significantly different from adult data. Warnings: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), DRESS, anaphylaxis and angioedema, hyponatremia, dizziness, gait/coordination disturbance, somnolence/fatigue, cognitive dysfunction, impaired vision, DILI

²

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Lacosamide (LCM)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO only (safety of IV formulation unknown in pediatric patients), BID Weight-based dosing pediatric pts <50 kg	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: dizziness and ataxia, cardiac rhythm and conduction abnormalities (prolonged PR, Atrial fibrillation and Atrial flutter), syncope, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),
Lamotrigine (LTG)	Adjunctive therapy in patients aged 2 years and older: - partial-onset seizures. - primary generalized tonic-clonic seizures. - generalized seizures of Lennox-Gastaut syndrome. Monotherapy in patients ≥16 years of age only.	2003 (pediatric adjunctive POS)	PO, BID Weight-based dosing for patients 2-12 years of age	Placebo-controlled efficacy trial in 199 patients aged 2 to 16 years. Primary efficacy endpoint: percentage change from baseline in all partial-onset seizures. The median reduction of all POS was 36% in patients treated with LAMICTAL and 7% on placebo (P<0.01).	Serious skin rash, including in pediatric patients (one death in controlled pediatric trials), TEN. Significant rash with concurrent valproate. Hemophagocytic Lymphohistiocytosis, DRESS, hematologic abnormalities (neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia), Aseptic Meningitis,
Levetiracetam (LEV)	Adjunctive therapy in the treatment of: - POS in patients one month of age and older with epilepsy - PGTCS in patients 6 years of age and older with idiopathic generalized epilepsy	2000 (4-17 years) 2012 (1 mo to 4 years) 2014 (IV)	PO/IV, BID Weight-based dosing in ped patients	1 mo to 4 yrs: RPCT evaluating the efficacy and tolerability in patients with refractory POS. Primary endpoint was responder rate, with statistically significantly greater number of responders on Keppra than on placebo	Warnings: Behavioral abnormalities and psychotic symptoms, somnolence and fatigue, anaphylaxis and angioedema, SJS and TEN, coordination difficulties, reduction in WBC and neutrophil counts (statistically sig worse in Keppra-treated pediatric patients than those on placebo), hypertension (particularly in the 1 mo to 4 yr study)

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Topiramate (TPM)	- Initial monotherapy in patients ≥2 years of age with POS or PGTCs - Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with POS or PGTCs	2009 (pediatric adjunctive POS)	PO, BID Weight-based dosing ages 2-9 yrs	Monotherapy: RCT (high dose [400 mg] vs low dose [50 mg] TPM) in pts ≥10 yrs with POS or PGTCs. Primary endpoint was between-group comparison of time to first seizure during the double-blind phase, which statistically favored the high dose. Monotherapy in pts 2-9 yrs was demonstrated via PK bridging. Adjunctive: 1 RPCT in POS patients 2-16 yrs and 1 RCPT in patients ≥2 yrs with PGTCs. Primary efficacy endpoint was median percent reductions in seizure rates compared to baseline, vs placebo. Both studies had statistically significant reduction in MSF.	Warnings for adult and pediatric patients: Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Cognitive/ Neuropsychiatric Adverse Reactions (lower in peds than adults), Hyperammonemia and Encephalopathy, Kidney Stones,

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Oxcarbazepine (OXC)	• Monotherapy in the treatment of partial seizures in children 4-16 years • Adjunctive therapy in the treatment of partial seizures in children 2-16 years	2000 (adjunctive use in pediatric POS)	PO, BID Weight-based dosing ages 2-16	Monotherapy – 4 RPCTs demonstrated efficacy in patients ages 8 and older primarily using study exit due to seizure as the efficacy measure. A 5th study in patients 1 mo to 16 years did not demonstrate efficacy, but this failure was felt to be due to design flaws, not lack of efficacy Adjunctive POS: 3 efficacy trials incl. pediatric patients (15 to 66 yrs, 3-17 yrs, and 1 mo to 4 yrs). Primary efficacy endpoint was between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase for the 2 RCPTs, both of which favored OXC over placebo. For the 3rd pediatric trial (1 mo to 4 yrs) the 1^o endpoint was change in seizure frequency per 24 hours compared to the seizure frequency at baseline, which also statistically favored OXC, but no evidence of effectiveness below age 2 yrs.	Hyponatremia, Anaphylactic Reactions and Angioedema, SJS and TEN (both seen in children and adults), DRESS, hematologic abnormalities, risk of seizure aggravation (especially PGTC) Cognitive/Neuropsychiatric Adverse Reactions (cognitive slowing, somnolence, coordination abnormalities) seen in pediatric patients,
Valproate, Valproic Acid (VPA)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures, ages 10 yrs and older		PO/IV, TID or BID depending on formulation	2 RPCTs in patients (patient ages not identified), primary endpoint was reduction in seizures compared to baseline vs placebo, with statistically significant difference.	Hepatotoxicity (including fatalities) particularly in patients < 2 yrs and in first 6 mos of treatment. Other warnings: Birth defects, Pancreatitis, thrombocytopenia, hyperammonemia, hypothermia, somnolence

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
Gabapentin (GBP)	Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy	2000 (adjunctive use in pediatric POS)	PO, TID Weight-based dosing for patients 3-11 years of age	Placebo-controlled efficacy trial in 247 pediatric patients with POS. Comparison of response ratio to placebo statistically significant (-0.146 vs -0.079) but responder rate not significantly different (frequency)	Somnolence and sedation, dizziness, DRESS In pediatric patients: Neuropsychiatric Adverse Reactions (emotional lability, hostility and aggression, concentration issues, and hyperkinesia)
Tiagabine (TGB)	Adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures		PO, BID	3 RPCTs with primary endpoint of median reduction in seizure frequency in patients with POS (statistically favored TGB over placebo)	Cognitive/Neuropsychiatric Adverse Events (impaired concentration and somnolence), Generalized Weakness, serious rash
Felbamate	recommended for use only in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is deemed acceptable in light of the benefits conferred by its use.		oral, divided doses 3 or 4 times daily	has been studied as monotherapy and adjunctive therapy in adults and as adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome. "Adults 14 years of age and older"; The majority of patients received 3600 mg/day in clinical trials evaluating its use as both monotherapy and adjunctive therapy.	Boxed Warning for Aplastic anemia and Hepatic Failure
phenobarbital	Generalized tonic-clonic and partial seizures in patients of any age		Oral, 2 to 3 divided doses		CNS depression- sedative effect, hypersensitivity reaction, Steven's Johnson syndrome and toxic epidermal necrolysis.
phenytoin	indicated for the treatment of tonic-clonic (grand mal) and If occurs, follow-up observation is psychomotor (temporal lobe) seizures and treatment of seizures occurring during or following neurosurgery		Oral, 2 to 3 divided doses. Once a day may be considered with Dilantin Extended release		hypersensitivity reaction, Steven's Johnson syndrome and toxic epidermal necrolysis. DRESS- Drug reaction with Eosinophilia and Systemic Symptoms, Multiorgan hypersensitivity. Hematopoietic complications. Acute hepatotoxicity

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
pregabalin	Adjunctive treatment for the treatment of partial onset seizures in patients 1 month of age and older	5/3/2018- POS age 4 and older, 5/23/2019 POS age 1 month and older	oral, 2 to 3 times / day	The efficacy of LYRICA as adjunctive therapy in partial-onset seizures was established in a 12-week, randomized, double-blind, placebo-controlled, multicenter study in pediatric patients 4 years to less than 17 years of age with partial-onset seizures with or without secondary generalization. The efficacy of LYRICA as adjunctive therapy in partial-onset seizures was established in a 14-day, randomized, double-blind, placebo-controlled, multicenter study in children 1 month to less than 4 years of age with partial-onset seizures with or without secondary generalization. The youngest patient evaluated was 3 months of age	Angioedema, hypersensitivity reactions dizziness and somnolence
zonisamide	indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy	none	oral , once daily	The effectiveness of ZONEGRAN as adjunctive therapy (added to other antiepilepsy drugs) has been established in three multicenter, placebo-controlled, double blind, 3-month clinical trials (two domestic, one European) in 499 patients with refractory partial onset seizures with or without secondary generalization	Serious skin reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS-drug reaction with eosinophilia and system symptoms/ multiorgan hypersensitivity. Oligohidrosis and Hyperthermia in pediatric patients. Metabolic acidosis. Cognitive adverse effects: somnolence, difficulty with concentration, speech or language problem

Clinical Review
 Steven Dinsmore, DO
 NDA 212839 (cenobamate) XCOPRI

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
carbamazepine	Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types. Generalized tonic-clonic seizures (grand mal). Mixed seizure patterns which include the above, or other partial or generalized seizures		Oral, 2 to 4 times daily		Serious dermatologic Reactions, Stevens-Johnson syndrome, Toxic epidermal necrolysis. Associated with HLA-B*1502 Allele. Hypersensitivity reactions, DRESS and multiorgan hypersensitivity associated with HLA-A*3101 Allele. Anaphylaxis and Angioedema

Product (s) Name	Indication / Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues
vigabatrin	Refractory Complex Partial Seizures as adjunctive therapy in patients ≥10 years of age who have responded inadequately to several alternative treatments; SABRIL is not indicated as a first line agent. Infantile Spasms - monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.	12/11/2012 for Refractory Complex Partial Seizures in patients ≥10 years of age. Infantile Spasms - monotherapy in infants 1 month to 2 years of age.	Oral, twice daily	The effectiveness of SABRIL as adjunctive therapy in adult patients was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies. A total of 357 adults (age 18 to 60 years) with complex partial seizures, with or without secondary generalization were enrolled. SABRIL was studied in three double-blind, placebo-controlled, parallel-group studies in 269 patients who received SABRIL and 104 patients who received placebo. No individual study was considered adequately powered to determine efficacy in pediatric patients age 10 years and above. The data from all three pediatric studies were pooled and used in a pharmacometric bridging analysis using weight-normalized doses to establish efficacy and determine appropriate dosing. All three studies were randomized, double-blind, placebo-controlled, parallel-group, adjunctive-treatment studies in patients aged 3-16 years with uncontrolled complex partial seizures with or without secondary generalization. The effectiveness of SABRIL as monotherapy was established for infantile spasms in two multicenter controlled studies.	permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, SABRIL may also decrease visual acuity. Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing. available only through a restricted program called the Vigabatrin REMS Program

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cenobamate is not authorized for sale in any country as of November 20, 2019³.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Key Regulatory History
12/22/06	Sponsor submitted a new IND
1/26/07	IND was placed on a Full Clinical Hold (seizures in monkeys associated with the administration of YKP3089. In one such study (14-day oral toxicity study in cynomolgus monkeys) this occurred following a second dose of 60 mg/kg.)
6/18/07	IND was placed on a Partial Clinical Hold (dose limited to 250mg)
3/28/08	We removed the Partial Clinical Hold (basis unclear, Clinical Hold Response/Complete correspondence on paper)
2/2/11	Type B, EOP1 meeting - To discuss design and conduct of Study YKP3089C013
5/24/13	SPA-1 (carcinogenicity study) – Agreement
11/6/13	SPA-2 (carcinogenicity study) - Agreement
8/7/14	Type C, Guidance Meeting - To discuss proposed clinical development plans
1/7/15	Sponsor submitted a Protocol/QT/IRT Study Protocol
5/15/15	Type B, EOP 2 Meeting – To discuss proposals and questions regarding CMC
5/26/15	Sponsor submitted a Protocol/QT/IRT Study Protocol
10/14/15	Type B, EOP 2 Meeting – To discuss the results of completed non-clinical and clinical studies and to obtain feedback regarding nonclinical and clinical development plans for their NDA submission
11/24/15	Sponsor submitted an initial Pediatric Study Plan-1
11/25/15	IND was placed on a Partial Clinical Hold- DRESS syndrome case identified, no new enrollments, continue patients with ongoing treatment 4 months or longer, Identify safety strategy, search safety dataset for additional cases
2/26/16	IND was placed on a Continue Partial Clinical Hold- allow new enrollment, maximum dose 200mg
5/18/16	IND was placed on a Continue Partial Clinical Hold- allow maximum dose 400mg
9/22/16	Meeting Request Denied – To discuss the study design for the human abuse liability study and whether a formal drug dependency study is needed.
10/27/16	IND was placed on a Continue Partial Clinical Hold- HAL, Human Abuse Liability Protocol, may not proceed due to a maximum single dose of 600mg. We are also notifying you that we have concluded that all pediatric age groups (i.e., birth up to 17 years) must be excluded from YKP3089 clinical studies, even at doses that are otherwise consistent with the conditions of the partial hold.
11/12/17	Sponsor submitted an initial Pediatric Study Plan-2
5/9/17	We provided a written response for their initial Pediatric Study Plan-2
5/18/17	Type C, Guidance Meeting – To discuss the Continue Partial Hold
7/21/17	Agreed Initial Pediatric Study Plan-2
8/8/17	Agreed Initial Pediatric Study Plan-2
8/10/17	Agreed Initial Pediatric Study Plan-2
8/21/17	We issued a Pediatric Study Plan Initial Agreement letter

³ Identified as “new drug in development” on the Epilepsy Foundation, “Epilepsy Pipeline Tracker”

Date	Key Regulatory History
3/16/18	Type C, Guidance Meeting – To discuss the Chemistry, Manufacturing and Controls (CMC) and nonclinical aspects
5/3/18	Type B, Pre-NDA Meeting – To discuss the potential submission of an NDA
5/30/18	VAI letter issued
11/21/18	New NDA submitted

3.3. Foreign Regulatory Actions and Marketing History

None

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)⁴

Clinical site inspections are addressed in the Data Quality and Integrity sections of the Individual trials sections 6. No protocol deviations were of sufficient magnitude to impact the clinical study outcome.

There was a procedural data capture issue that caused seizure diary data discrepancies. Data discrepancies were due to the inability of the eCRF system to accept daily seizure counts >99. Based on this finding, an information request was sent to the sponsor asking whether any additional subjects had daily seizure counts >99 during this study. The sponsor identified three subjects participating in Protocol YKP3089C017 with daily seizure counts >99. The Biometrics reviewer integrated the corrected seizure counts into the statistical review, and the previous conclusion of efficacy was not altered.

There was an issue of database lock and unlock in protocol C017. The database had been unlocked on four separate occasions after the database hard lock date. The sponsor and CRO inspections were conducted to evaluate the processes in place for database locking and unlocking and to investigate any changes made to the database after the hard lock date. As part of this process, audit trails were requested from the sponsor. Review of the audit trails focused on changes to the seizure diary data (the primary efficacy endpoint) and adverse events. Other than the removal of the duplicate seizure count (see below) in one subject, no other significant changes were noted.

(b) (4) was responsible for the database hard lock and subsequent unlocks; both of which required sponsor approval. The sponsor had disclosed four dates of approvals provided for

⁴ From "Overall Assessment of Findings and Recommendations, Clinical Inspection Summary, Division of Clinical Compliance Evaluation, Office of Scientific Investigations.

database unlocks involving seven subjects. One of these database changes involved the deletion of a seizure entered in both the double-blind and open-label phases of the study.

The end of study visit for the double-blind phase (Visit 9) was also the same visit as the first visit for the open-label phase. The sponsor confirmed that seizures occurring on the last day of the double-blind period were not counted in the double-blind phase but rather were included in the open label phase. A review of all seizures occurring on the last day of the double-blind phase was performed in order to evaluate whether not counting seizures occurring on the last day of the double-blind phase in that phase of the study introduced any potential bias. This review confirmed some treatment arm imbalances for seizures occurring on the last day of the double-blind phase, but not in favor of the study drug.

4.2. **Product Quality**

The Office of Product Quality (OPQ) review team recommends that the Agency approve NDA 212839 for XCOPRI (cenobamate) tablets. From a quality perspective, the application provides adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use by the intended patients.

4.3. **Clinical Microbiology**

N/A

4.4. **Nonclinical Pharmacology/Toxicology**

The nonclinical team concludes that “The application is approvable from a pharmacology/toxicology standpoint. A repeat embryofetal development study in rat should be conducted as a postmarketing requirement.”

4.5. **Clinical Pharmacology**

4.5.1. **Summary of Clinical Pharmacology and Pharmacokinetics** (from OCP Review)⁵

Mechanism of Action (MOA): Cenobamate reduces repetitive neuronal firing by enhancing the fast and slow inactivation of sodium channels and by inhibiting the persistent component of the sodium current. It is also a positive allosteric modulator of six subtypes of the γ aminobutyric acid (GABAA) ion channel. However, the exact mechanisms by which cenobamate exerts its anticonvulsant effect in humans is unknown.

⁵ OCP Integrated Review, Section 3.2, Page 8

Dose Proportionality: The pharmacokinetic parameters of cenobamate increased in a greater than dose-proportional manner following single oral doses of escalating strength, ranging from 5 mg to 750 mg. However, the C_{max} of cenobamate increased in a dose proportional manner. The PK of cenobamate was essentially dose proportional following multiple doses ranging from 50 mg/day to 500 mg/day.

Variability: Inter-subject variability of cenobamate in humans was up to 25% for C_{max} and up to 35% for AUC_{0-t}. The intrasubject variability of cenobamate was estimated to be 14% for C_{max} and up to 5% for AUC_{0-t}.

Absorption: Cenobamate was well absorbed, based on mass-balance study demonstrating that at least 88% was recovered in urine following oral administration. Co-administration with a high-fat meal showed no significant effect on the rate and the extent of absorption.

T_{max}: The median cenobamate T_{max} 1 to 4 hours after single- or multiple-dose administration under fasted condition over the range of 10 to 400 mg.

Distribution: Plasma protein binding of cenobamate is moderate (60%) and independent of concentration. Cenobamate mainly binds with human albumin protein and not with α 1-acid glycoprotein. Cenobamate is mainly confined to plasma. The whole blood to plasma ratio of cenobamate was 0.6. The estimated volume of distribution was 40 L to 50 L.

Metabolism: Cenobamate is extensively metabolized in liver, primarily by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5.

There were no major circulating metabolites (i.e., >10% of total drug related material) identified in human plasma. In a mass-balance study, administration of radiolabeled cenobamate, unchanged cenobamate accounted for >98% of the total AUC of radioactivity in plasma. M1 (N-glucuronide of cenobamate) was the only metabolite found in human plasma, and the exposure (AUC) of M1 was found to be 1.2% of the parent drug. In urine and feces, the N-glucuronide metabolite (39.4% of the dose), oxidative O-phenyl glucuronide (20.4% of the dose), dihydrodiol and its glucuronide (17.1% of the dose), and side chain O-glucuronide (3.9% of the dose) appeared to be the major metabolite of cenobamate in vivo. Unchanged cenobamate accounted for 6.8% of the dose which was mainly excreted in the urine (6.4%).

Excretion: Following administration of radiolabeled cenobamate, a mean of 93.0% of the total radioactive dose was recovered in urine (87.8%) and feces (5.2%). The mean terminal half-life for cenobamate ranged from 50 to 60 hours following single oral doses of 100 to 400 mg.

4.5.2. Dose Response

The OCP reviewer created plots of change from baseline seizure frequency by study epochs in titration and maintenance dose periods and dose arms to examine the effect of treatment over time. This analysis reveals a trend of increased effectiveness as the treatment interval progresses through titration into maintenance periods in study C013 (Figure 2) and C017 (Figure 3).

Figure 2 Percent Change from Baseline Monthly Seizure Frequency by Arm and By Time Period in Phase 2 Study C013

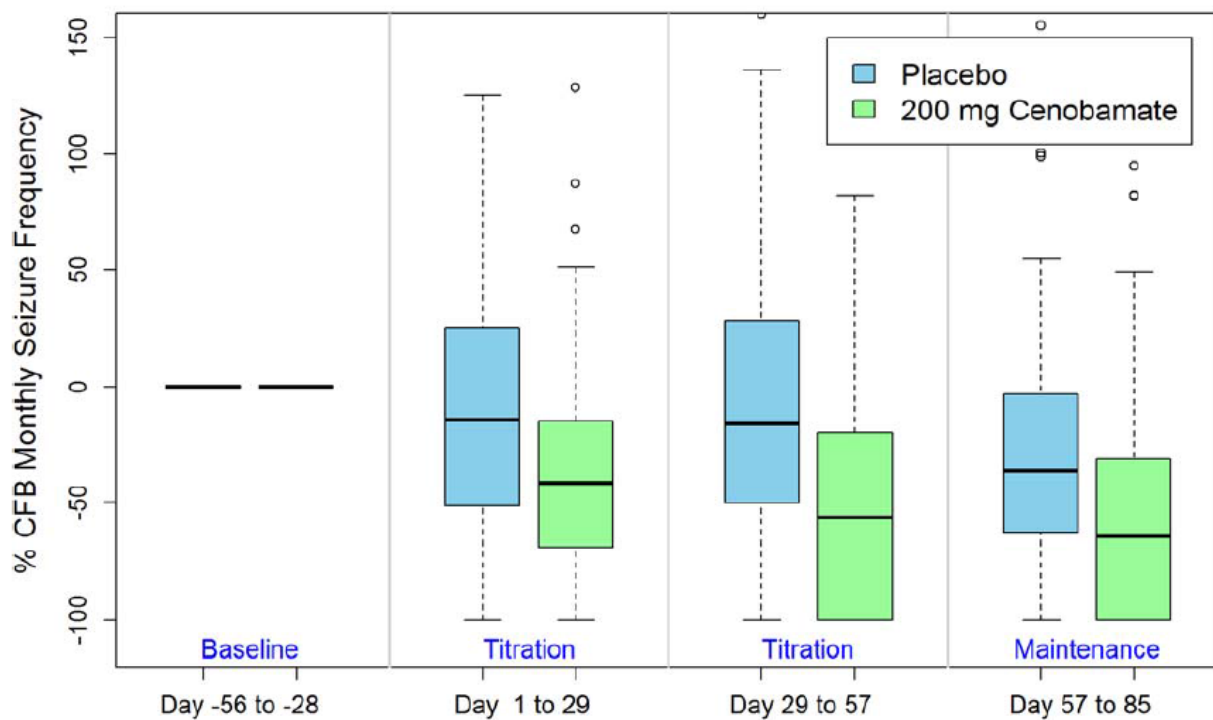
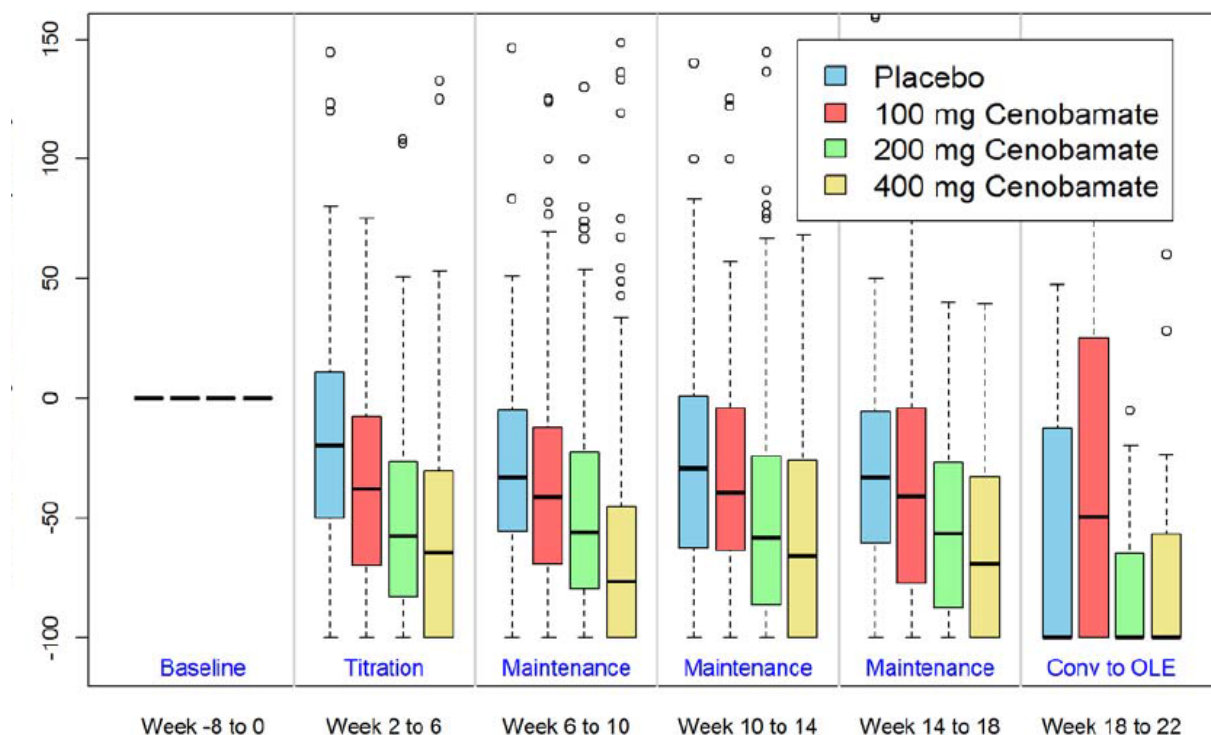


Figure 3 Percent Change from Baseline Monthly Seizure Frequency by Arm and By Time Period in Phase 3 Study C017



Titration Rate vs Clinical Efficacy

The pivotal study titration rates were more rapid than in study C021 from which the rate in proposed labeling is derived. This slower rate of dose escalation will result in a shift of the desired therapeutic effect to later in the titration schedule. The OCP reviewer conducted an independent analysis to compare the pivotal study titration scheme to the modified schedule of reduced escalation rate in proposed labeling. The analysis examined concentration time profile, [Figure 4](#), and the seizure frequency compared to titration regimen, [Figure 5](#). This analysis is valuable to determine how the reduced dose escalation rate and the prior titration schedules map to each other over the titration timeline. The OCP reviewer concludes that “The slower titration scheme proposed for the label can be expected to produce approximately half the maximum effect by 5 weeks and maximum effect at 14 to 18 weeks.” In addition, on visual inspection of the graphic analysis of [Figure 5](#), a therapeutic effect in the range of the 100mg treatment arm of study C017, see [Table 11](#), is expected to be present at approximately 7 weeks of titration.

Figure 4 Predicted Mean Plasma Concentration-Time Profile For Both Titration Regimens

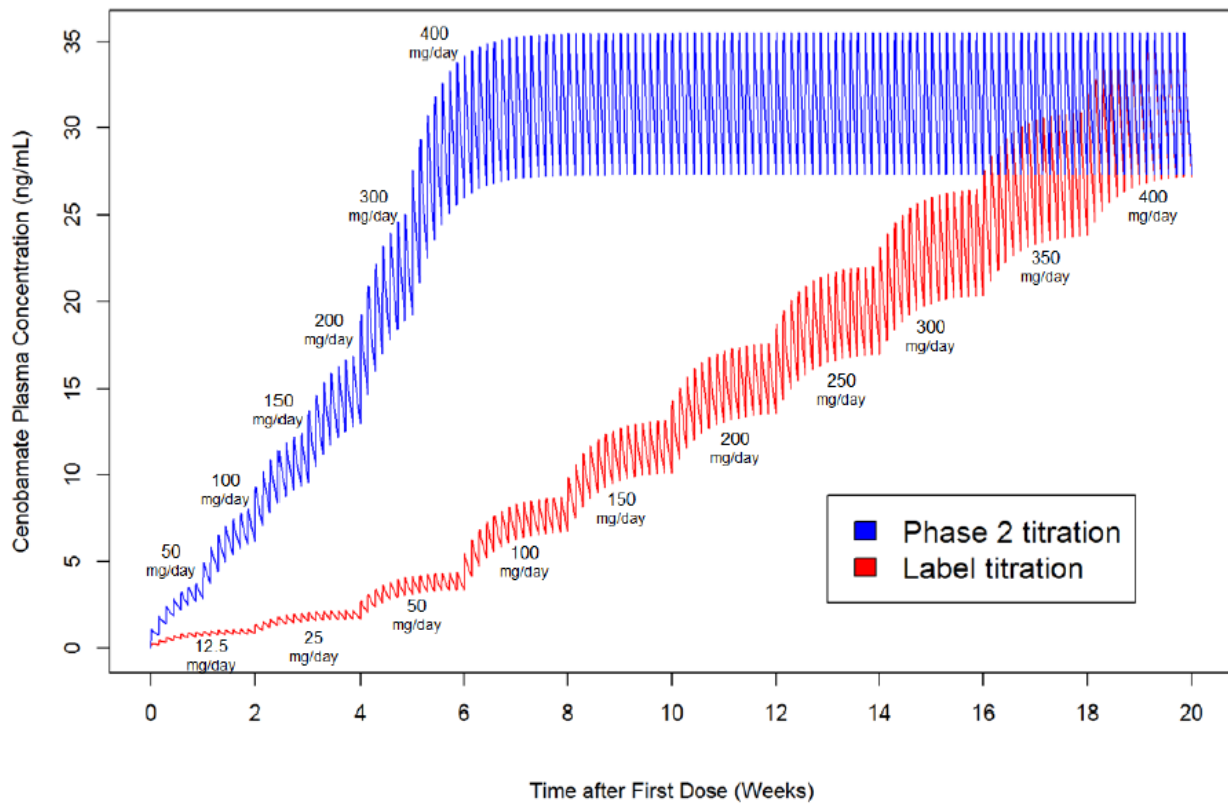
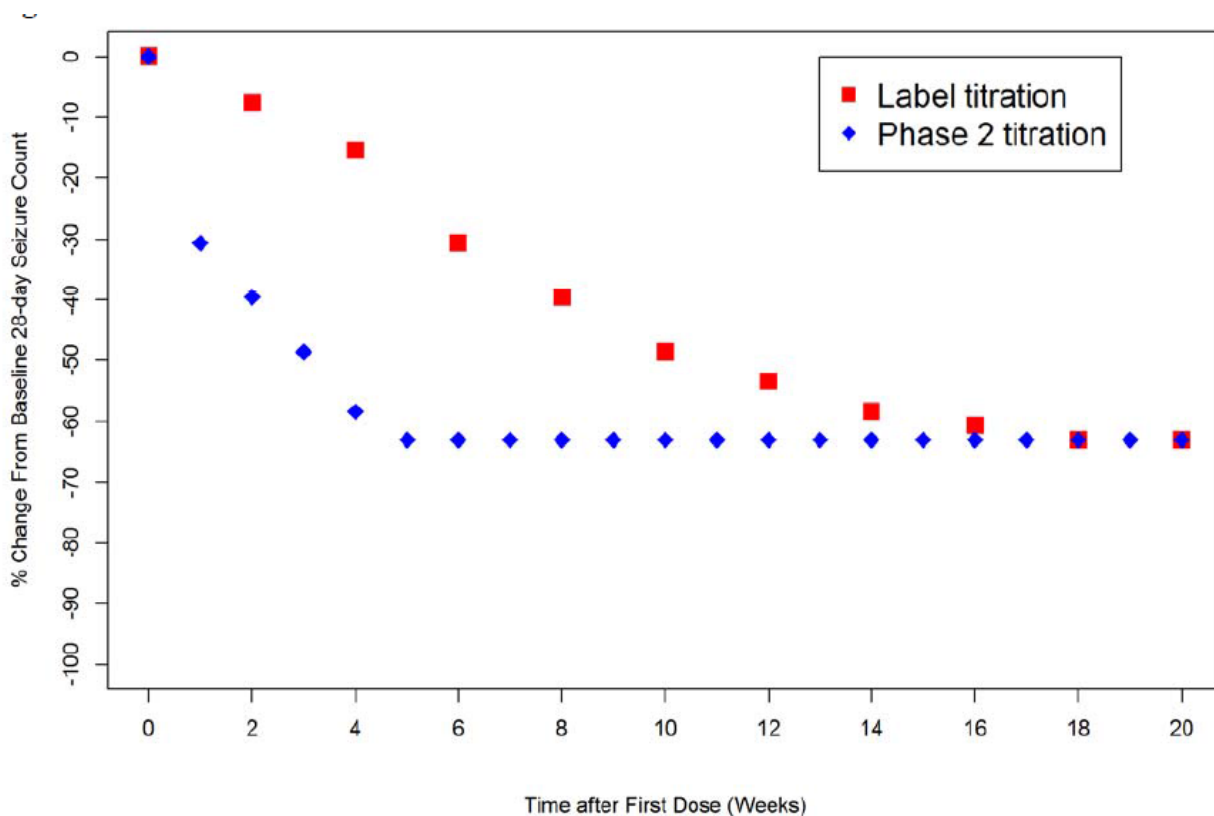


Figure 5 Predicted Change from Baseline 28-day Seizure Rate for Both Pivotal Study and Study C021 (proposed labeling) Titration Regimens



4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

None

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Sample Table. Listing of Clinical Trials Relevant to this NDA/BLA [Replace this title with a Table Caption using the *Insert Caption* button in the CRT tab.]

Trial Identity	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
C013	01397968	Multicenter, double blind, randomized, placebo controlled. 8-week baseline seizure frequency. 3 seizure / 28 eligible. 6-week titration to 200mg YKP daily- 50mg x 2 wk, 100mg x 2 wk, 150mg x 2 wk then target 200mg for additional 6 wk. <i>Study Period 7/6/11 to 6/15/13</i>	Placebo / 200mg Daily	% Change in Sz Frequency per 28 days, Baseline to Treatment	6 wk titration ,6 wk maintenance, Follow 21 day after EOT	PBO 109 YKP (200mg) 113	Age 18-65 M/F Refractory Partial Epilepsy Stable 1-3 AEDs	40 Centers 4 Countries (US, India, Rep. Korea, Poland)
C017	01866111	Multicenter, double blind, randomized, placebo controlled, 8 wk. baseline to determine Sz frequency, eligible 8 POS during baseline, minimum 3 / 4 weeks. 6 wk titration, start 50mg/day, escalate 50mg/wk to 200mg, then 100mg/wk in the 400mg dose arm. Then 12 wk double blind maintenance interval. <i>Study period 7/31/13 to 6/22/15</i>	Placebo 100mg 200mg 400mg	% Change in Sz Frequency per 28 days, Baseline to Treatment	6 wk titration, 12 wk maintenance	PBO 108 100mg 108 200mg 110 400mg 111	Age 18-70 years Uncontrolled Sz, failed at least 1 AED within 2 years. Stable on 1-3 AEDs for min. 4 wk	107 centers Enrolled in 16 countries
-								
Studies to Support Safety								
C021	02535091	Open label, Safety and PK study Study or reduced dose escalation rate during titration to assess DRESS risk. 07/2016- 12/2020	Daily up to 400mg		12 month with subsequent participation at discretion of investigator	Dose may be titrated to 400mg be investigator discretion	Age 18-70 years, Partial epilepsy uncontrolled with treatment of at least on AED in past 2 years. Stable dose of 1-3 AEDs for 3wks	137 Centers 17 countries

Table 2 Phase 1 Studies Reviewed for Safety, Healthy Volunteer Subjects

STUDYID	dosing	Design	purpose	peak dose	Study Duration	n -PBO	n- YKP	post YKP Study day (*, *= washout)	YKP Treatment Duration
AA22780	single dose (SAD)		PK	750	1	33	77	2	1
AA24143	MAD		PK	200	17	15	35	14	14
AA39450	single dose	Crossover	BE food	300	22	0	16	2, 22	1
AA40616	single dose		photosensitivity	400	3	0	12	2	1
AA41857	single dose (SAD)		mass balance	400	1	0	6	2	1
YKP3089C006	multiple dose, 1/pd	1 sequence, 3 Period	PK-contraceptive	100	35		28	35	30
YKP3089C009	MAD		PK 250-300mg	300	17	6	14	18	17
YKP3089C010	PK	1 sequence, 3 Period	PK DDI YKP-VPA	150	19		16	26	20
YKP3089C011	PK	1 sequence, 3 Period	DDI, YKP-CBZ	200	25		16	40	25
YKP3089C014	PK	1 sequence, 2 Period	DDI, YKP-CBZ-Metabolism	200	42		16	43	14
YKP3089C016	PK	1 sequence, 4 period	DDI, YKP-PHT	200	69		16	70	28
YKP3089C018	MAD	3 sequence, 4 period	PK titration	600	29	9	21	30	29
YKP3089C019	single dose	1 sequence, 2 period	BE Tablet	100	28		14	2	1
YKP3089C020	multiple	3 sequence, 3 Period	TQT	500	65	54	52	66	64
YKP3089C022	50mg-200mg, step 50	1 sequence, 2 Period	DDD, YKP-PB	200	62		16	56	35
YKP3089C024	single dose 200mg and 400mg YKP to compare to alprazolam with 16 day washout	10 sequence, 5 way	abuse potential	400				2, 17	1
YKP3089C026	multiple	1 sequence	DDI, P450 probe	200	109	0	24	110	98
YKP3089C027	Single dose		hepatic impairment	200	6		24	2	1
YKP3089C028	single dose		renal impairment	200	6		31	2	1
YKP3089C029	single dose (SAD)	4-way crossover	ETOH interaction	200	63		30	0	
YKP3089C030	single dose		Age Effect on PK	200	12	0	26	2	1

5.2. Review Strategy

Examination of irregularities including protocol violations were performed to guide OSI site investigation. Also considered in site investigation were high volume study site recruitment and disproportionate contribution to the efficacy outcome. Distribution of study population demographics across placebo and treatment arms was examined. The trial design was assessed and is similar to the design of approved drugs for partial onset seizure treatment. The statistical reviewer was able to perform an independent review using the Applicant's submitted datasets and confirmed the Applicant's analysis results.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. C013

6.1.1. Study Design

Overview and Objective

The primary objective of this study is to evaluate the efficacy of YKP3089 at dosages up to 200 mg/day in reducing seizure frequency when compared to baseline in subjects with partial onset seizures not fully controlled despite their treatment with 1 to 3 concomitant AEDs.

Trial Design

This is a multicenter, double-blind, randomized, placebo-controlled study, with an 8-week baseline, 6-week titration and 6-week maintenance phase. This is followed by a 1-week taper period for subjects who are taking 100, 150 or 200mg of YKP3089.

Baseline seizure frequency is captured by an 8-week seizure diary documentation of seizure frequency. If the subject maintains an excellent prospectively created seizure diary on either a written or electronic calendar that can be presented to the study staff and approved by the sponsor or their designee, then this can be used for a 4-week retrospective baseline, which will be combined with a 4-week prospective baseline. If no such documentation is available, an 8-week prospective baseline is required.

Study drug (cenobamate) 50mg will be taken once daily in the morning (with or without breakfast) for two weeks. If there is good tolerability for 14 days dose will be advanced to 100mg (or placebo) daily beginning day 15. If the 100mg dose is well tolerated for 14 days, then cenobamate will be increased to 150mg on day 29. If the 150mg dose has good tolerability for 14 days, then the dose will increase to 200mg a day. Patients who report side effects may remain on the same dose (50mg, 100mg, 150mg, or placebo) and delay titration until the next visit.

After day 43 (day of achieving 200mg dose) the patient will be called one week later to assess tolerability. In the event of poor tolerability, the dose may be reduced by 50mg during the telephone contact. This should be followed by an unscheduled visit. Following day 43 patients will continue treatment an additional 6 weeks, until day 85. Patients have a follow up visit at day 106.

Dose Reduction

A dose reduction can occur at a visit during titration, maintenance, open-label extension or during the phone contact. Subjects who have had their dose increased and subsequently fail to meet good tolerability criteria (as described in the section below) will have their dose decreased. Dose adjustments require an unscheduled visit. If the patient is unable to tolerate 50mg, he/she will be discontinued at the discretion of the investigator. Subjects whose dose was decreased may not have their dose increased again during the double-blind period.

Study Endpoints

Primary Endpoint

Percent change in seizure frequency per 28 days in the Treatment Period compared to the Baseline in the ITT Population. Last-observation-carried-forward (LOCF) method will be used to impute for missing data for subjects who withdraw from the study early. Seizure frequency will be based on number of seizures per 28 days, calculated as the number of seizures over the entire time interval divided by the number of days in the interval and multiplied by 28. Analysis will be conducted using rank ANCOVA with treatment, study region (such as site or country) as factors, and the baseline seizure frequency as a covariate.

Secondary Endpoint

Responder rate: An analysis of subjects who experience a 50% or greater reduction in seizure frequency in the Treatment Period of the Double-Blind Phase.

Statistical Analysis Plan

Statistical Analysis Plan Amendment 3 dated 26 July 2013

Primary Efficacy Variable

Seizure Counts

The primary efficacy variable is the partial seizure frequency per 28 days.

Partial seizure frequencies (average monthly [28-day] partial seizure rates) for each study

period (baseline, double-blind period) will be calculated by summing the number of seizures in each period and dividing by the total duration for that period (i.e., number of days in that period) excluding days with “no data available” as per seizure diary, and multiplying by 28 in order to normalize to a 28-day rate.

Any seizure cluster where individual seizures cannot be counted will have a seizure count of “1” assigned.

Baseline seizure frequency will be calculated using the 56 days prior to Study Day 1 (randomization date) excluding days with “no data available” in the seizure diary.

To calculate the on-treatment seizure frequency, the days utilized will be Study Day 1 (randomization date) through the last day of the double –blind treatment excluding all dose tapering days (or a subset depending on the specified analysis) and days with “no data available” in the seizure diary.

Partial seizures are defined as the total of simple partial with motor component (type B), complex partial seizures (type C) (-unique seizure types to be combined) and secondarily generalized tonic clonic-seizures (type C).

Partial seizures without a motor component (Type A) will not be analyzed.

Primary Efficacy Outcome

The primary efficacy outcome is defined as percent change (reduction) from baseline in seizure frequency during the double-blind period. Percent change (reduction) from baseline during the double-blind period will be calculated as follows:

Percent change (reduction) = (baseline seizure frequency rate per 28 days – double-blind period seizure frequency rate per 28 days) / baseline seizure frequency rate per 28 days x 100.

Sample Size Determination

A sample size of 100 subjects per treatment group will be able to detect a difference of 16% in median percent reduction in seizure frequency between an active dosage group and placebo group, at a two-sided significance level of 0.05, assuming a standard deviation of 40%. This sample size was estimated assuming 80% power with a two-sample Wilcoxon rank sum test used and assumed as the primary analysis.

Protocol Amendments

There were 6 protocol amendments following the initial protocol through the duration of the

active trial. Only protocol amendment 1 was substantive in potential influence on study outcome. This amendment allowed an additional cohort of epilepsy patients into the study that had previously been excluded due to treatment with concomitant carbamazepine. The reason for protocol amendment 1 was to allow patients on concomitant carbamazepine into the study. A DDI study had been completed that showed YKP, when added to carbamazepine therapy reduced the total carbamazepine & carbamazepine epoxide concentration by 20%. This level of carbamazepine reduction was considered low enough to allow these patients into the study.

Reviewer Comment: This modification could potentially increase seizure frequency if YKP reduced the concentration of the concomitant AED meaningfully. However, randomization should distribute this effect across treatment arms.

6.1.2. Study Results

Compliance with Good Clinical Practices

In the clinical study report the sponsor attests the study was conducted according to standards of Good Clinical Practice.

Financial Disclosure

Form 3454 is presented in the eCTD to certify that investigators in study C013 have no disclosable financial interests or arrangements.

Patient Disposition

There were 285 patients screened that resulted in 222 patient randomized into the study. There most frequent reasons patients did not reach randomization were due to failure to meet inclusion criteria or presence of exclusion criteria. Addition attrition was due to patient withdrawal, adverse event, lost to follow and "other", [Table 3](#) . The distribution of events between treatment arms is also shown in [Table 3](#). There was no notable difference in withdrawal / discontinuation events between treatment arms.

Table 3 C013 Patient Screening and Disposition

Disposition Event	N Patients
INFORMED CONSENT OBTAINED	285
Pre-Randomization Events	
ADVERSE EVENT	1
EXCLUSION CRITERIA MET	17
INCLUSION CRITERIA NOT MET	32
LOST TO FOLLOW-UP	1
OTHER	5
WITHDRAWAL BY SUBJECT	7

Final Total RANDOMIZED	222	
Disposition by Treatment Group		
	YKP	Placebo
Randomized	113	109
ITT population	113 (100%)	108 (99.1%)
Safety	113 (100%)	109 (100%)
Adverse event withdrawal	4 (3.5%)	4 (3.7%)
Lost to Follow up	2 (1.8%)	0
Protocol Violation	0	1 (0.9%)
Patient Withdrawal	5 (4.4%)	4 (3.7%)
Other	0	1 (0.9%)
Completed Double Blind	102 (90.3%)	99 (90.8%)
Withdrawn from double Blind (total)	11 (9.7%)	10 (9.2%)

Protocol Violations/Deviations

Protocol violations are examined. Eight are identified in an area that may influence study outcome. Four are in the category IP compliance. Two patients on cenobamate did not have their dose advanced beyond 50mg apparently due to clerical error. These were at site 110. In the next instance in the IP compliance category one patient in the YKP arm lost eight capsules of study drug and another patient lost 4 capsules. There were two instances involving seizure diary. In the first a patient in the placebo arm had no seizure diary at visit 6; the remediation for seizure record keeping is not provided. In the second, a patient in the cenobamate arm had no diary entry for a single day. There were two concomitant medication items. In the first a patient in the placebo arm was on concomitant diazepam for 6 weeks, in the second a patient in the placebo arm had levetiracetam added at visit 12 (last treatment visit).

None of the protocol violations involving study drug or concomitant medications favor the cenobamate treatment arm. The two seizure diary events also do not bias in favor of the cenobamate treatment arm.

Table of Demographic Characteristics

Examination of baseline features reveals an equal distribution of females and males in the study and across treatment arms. The mean and median patient age in the cenobamate treatment arm are 36.2kg and 36kg respectively while the mean and median ages in the placebo arm are 37.5kg and 38kg respectively. The racial distribution reveals a majority of “white” patients where the second most common racial group is “Asian”. The distribution of these two groups across the placebo and treatment arm is balanced. There is a small proportion of “black or African American” with a total of 2.25% of the total patients. These patients are adequately balance across treatment arms given the small number. There are 4 countries in study C013. The United States had the majority contribution in the study with 38.7% of patients while India, South Korea, and Poland contributed 23%, 18.5% and 19.8% respectively. The distribution of patients by national origin is balanced across the treatment arms, see [Table 4](#).

Table 4 C013 Population Demographics

Distribution by Treatment Arm						
Arm	Count	% of Total				
YKP3089	113	50.90%				
Placebo	109	49.10%				
All	222	100.00%				
Age						
Statistics	YKP3089	Placebo	Total			
N	113	109	222			
Mean	36.24	37.49	36.85			
Std Dev	11.27	11.38	11.31			
Min	18	18	18			
Quantiles25	26	27.5	27			
Median	36	38	37			
Quantiles75	44	46.5	45.25			
Max	61	59	61			
Demographics						
	Cenobamate		Placebo		Total	
Sex						
	# Patients	% Patients	# Patients	% Patients	Total Count	% of Total
F	58	51.30%	51	46.80%	109	49.10%
M	55	48.70%	58	53.20%	113	50.90%
All	113	100.00%	109	100.00%	222	100.00%
Race						
ASIAN	49	43.40%	45	41.30%	94	42.34%
BLACK OR AFRICAN AMERICAN	3	2.70%	2	1.80%	5	2.25%
UNKNOWN	3	2.70%	2	1.80%	5	2.25%
WHITE	57	50.40%	58	53.20%	115	51.80%
OTHER	1	0.90%	2	1.80%	3	1.35%
All	113	100.00%	109	100.00%	222	100.00%
Ethnicity						
HISPANIC OR LATINO	4	3.50%	3	2.80%	7	3.15%
NOT HISPANIC OR LATINO	105	92.90%	101	92.70%	206	92.79%
NOT REPORTED	4	3.50%	5	4.60%	9	4.05%
All	113	100.00%	109	100.00%	222	100.00%
Country						
IND	26	23.00%	25	22.90%	51	22.97%
KOR	22	19.50%	19	17.40%	41	18.47%
POL	22	19.50%	22	20.20%	44	19.82%
USA	43	38.10%	43	39.40%	86	38.74%

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The distribution of epilepsy characteristics is balanced across treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There are 13 entries from 13 patients for rescue medication where the medications were benzodiazepines. From among these patients there were 8 in the placebo arm and 5 in the cenobamate treatment arm. This profile of rescue medication use is balanced and is not expected to influence study outcome.

Efficacy Results – Primary Endpoint

The primary efficacy analysis demonstrated a statistically significant effect of cenobamate ($p < 0.0001$) compared to placebo on the primary endpoint of median percent reduction in the 28-day partial-seizure frequency in the ITT Population (55.6% reduction in the cenobamate group versus 21.5% reduction in the placebo group; [Table 5](#)).

Table 5 C013 Efficacy Results, Primary Endpoint

Efficacy Results ITT population	Cenobamate	Placebo
	n=113	n=108
Primary: Percent change from baseline in seizure frequency per 28 days during double-blind treatment period*		
Baseline median	7.5	5.5
Endpoint median	3.8	5.0
Percent change from baseline	55.6	21.5
P value†	<0.0001	
*As presented above in “Primary Efficacy Outcome”, seizure frequency is calculated as the number of seizures over the respective interval (baseline or treatment) divided by the number of days in the interval multiplied by 28.		
† p-value is based on a Wilcoxon rank-sum test assessing if the median percent change in seizure frequency for the treatment group is significantly different from the median percent change in seizure frequency for the placebo subjects.		

Data Quality and Integrity

Based on risk level assessment by OSI and concurrence by DNP two sites for clinical inspection were determined for study C013. Site 110 was located in Philadelphia, PA where 4 patients were enrolled in the placebo arm and 6 patients were enrolled in the cenobamate treatment arm. There were no screen failures identified. Site 209 located in Bangalore, Karnataka India. There were 15 patients enrolled, 7 in the placebo arm and 8 in the cenobamate treatment arm, no screen failures are identified. There was also an FDA Establishment Inspection of the sponsor for study C013.

The CIS overall findings (for both studies C013 & C017) noted inspectional observations at one of the clinical investigator sites (C017), as well as at the sponsor and CRO. These findings are unlikely to have a significant impact on overall study results. OSI concluded that the study data generated are considered acceptable and may be used in support of this NDA.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy analysis also demonstrated a significant number of responders ($\geq 50\%$ reduction from baseline in seizure frequency) in the cenobamate group compared to the placebo group (50.4% in the cenobamate group versus 22.2% in the placebo group).

Table 6 C013, Efficacy Results, Secondary Endpoint- Responder Rate

Secondary Endpoint: Responder rate of $\geq 50\%$ reduction from baseline in seizure frequency during double-blind treatment period		
Efficacy Results ITT population	Cenobamate	Placebo
mITT Population*	n=106	n=102
$\geq 50\%$ Responder, n (%)	53 (50%)	22 (21.6%)
*maintenance phase		

Dose/Dose Response

See Section [7.1.4 Dose and Dose-Response](#)

Durability of Response

See Section [7.1.5, Onset, Duration, and Durability of Efficacy Effects](#)

Persistence of Effect

See Section [7.1.5, Onset, Duration, and Durability of Efficacy Effects](#)

Additional Analyses Conducted on the Individual Trial

none

6.2.C017

6.2.1. Study Design

Overview and Objective

The primary objective of this study is to evaluate the effective dose range of YKP3089 at dosages from 100mg up to 400 mg/day in reducing seizure frequency when compared to baseline in subjects with partial onset seizures not fully controlled despite their treatment with 1 to 3 concomitant AEDs.

Trial Design

This is a multicenter, double-blind, randomized, placebo-controlled study with an 8-week prospective baseline and an 18-week double-blind treatment period (including a 6-week titration phase and 12-week maintenance phase), followed by a 3-week blinded study drug taper period (for subjects leaving the study) or a blinded 2-week conversion period (for subjects participating in the open-label extension), with a final follow-up visit 2 weeks after the last dose of study drug.

Subjects who meet all inclusion criteria and none of the exclusion criteria will first undergo an 8-week baseline to assess seizure frequency. Subjects who have experienced at least 8 seizures during the baseline period without a seizure-free interval of greater than 25 days any time during those 8 weeks will be randomly assigned in a 1:1:1:1 ratio to receive placebo or YKP3089 100, 200, or 400 mg given once per day in the morning. Subjects must have at least 3 partial seizures during each of the two consecutive 4-week periods of the baseline. See timeline of assessments in [Table 7](#).

Subjects will first enter a 6-week titration phase, during which the initial dose will be 50mg/day. The planned increase in the daily dose will be 50mg/day/week increments until 200mg is reached and after which the dose will be increased by 100mg/day/week in subjects randomized to 400mg/day. See titration schedule in [Figure 8](#). Subjects will then enter a 12-week double-blind maintenance phase.

Table 7 C017, Study Timeline and Assessments

Visit windows of ± 2 days are allowed for visits 1 through 6	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or Early Termination ^a	Visit 10
	Baseline Seizure Count		Safety baseline	Titration Phase (Day 2-43)			Maintenance Phase (Day 44-127)			
visit windows of ± 3 days are wed for visits 7 through 10	Day-56	Day-28	Day 1 ^l	Day 15 ^m	Day 29 ^m	Day 43	Day 71	Day 99	Day 127	Day 162
Assessment										
Informed Consent	X									
Inclusion / Exclusion	X		X							
Dispense/Review/collection of seizure diary	X	X	X	X	X	X	X	X	X	X
Randomization			X							
Dispense study Drug			X	X	X	X	X	X	X	
Drug Accountability				X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
a Subjects who do not plan to enter the optional open-label phase will have a blinded study drug taper. Subjects who plan to enter the open-label phase will have a blinded crossover at the beginning of the open-label phase.										
m Subjects will be contacted by phone on Days 8, 22 and 36 to assess tolerability and the occurrence of any early treatment-emergent adverse events and to reinforce compliance										

Study Endpoints

The primary efficacy endpoint to be evaluated for registration in the United States and the Rest of the World is the percentage change from the pretreatment baseline phase in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor, complex partial, or secondarily generalized seizures compared with the seizure frequency in double-blind treatment period.

The baseline seizure rate (B) is calculated by counting the number of seizures over the baseline period and dividing by the number of days in the interval with non-missing seizure data and then multiplying by 28. The double-blind period seizure rate (D) is calculated in a similar manner. The percentage change is equal to $100 \times (D-B)/B$. Simple partial seizures without a motor/visual component will not be counted in seizure frequency rates.

Percentage change in seizure frequency will be undefined if $B=0$. For the primary efficacy analysis, there will not be any baseline values with zero seizures due to inclusion criteria requirements. However, for the analysis of seizure sub-types, there is a possibility that B may be zero.

Statistical Analysis Plan

Statistical Analysis Plan Amendment 2 dated 20 March 2015

Protocol Amendments

There were 2 protocol amendments following the original protocol on 6/12/13. Amendment 1 of 1/7/14 provided results from a multiple ascending dose study up to 600mg a day (proposed C017 dose did not change). The results of study C013 were also included in the updated protocol. Initial starting dose was reduced to 50mg to improve tolerability. There was a revision of data monitoring committee review. Amendment 2 of 3/20/15 removed the interim analysis, added details of the statistical procedures and added lacosamide as a concomitant medication to have PK analyses.

6.2.2. Study Results

Compliance with Good Clinical Practices

In the clinical study report the sponsor attests the study was conducted according to standards of Good Clinical Practice.

Financial Disclosure

Form 3454 is presented in the eCTD to certify that investigators in study C017 have no disclosable financial interests or arrangements.

Patient Disposition

There were 533 patients screened that resulted in 437 patients randomized into study C017. There were 360 patients that completed the study. The most common reason for study withdrawal was an adverse event in 55 patients. The next most frequent reason for not completing the study was withdrawal by the patient. Addition attrition was due to, “lost to follow up”, “protocol violation”, “other” and “pregnancy”. Withdrawal due to adverse events had a dose related trend while there was no differentiation between treatment arms for other categories of withdrawal, [Table 8](#).

Table 8 C017 Patient Screening and Disposition

DSDECOD	Treatment Arm				Randomization Failure			Total
	PBO	100mg	200mg	400mg	Not Assigned	Not Treated	Screen Failure	
INFORMED CONSENT OBTAINED	106	108	110	112	13	1	83	533
RANDOMIZED	106	108	110	112		1		437
COMPLETED	93	95	90	82				360
Reason for Withdrawal								
ADVERSE EVENT	5	12	15	23				55
LACK OF EFFICACY		1		1				2
WITHDRAWAL BY SUBJECT	4		4	3		1		12
PROTOCOL VIOLATION			1	1				2
LOST TO FOLLOW-UP	1						2	3
OTHER	3			1				4
PREGNANCY				1				1

Protocol Violations/Deviations

The ADDV (protocol deviation analysis dataset) was examined. There were 16 entries from 15 patients in the “major” violation category. There were none in the placebo arm, with 5 (4.6%), 3 (2.7%), and 7 (6.3%) in the 100mg, 200mg and 300mg treatment arms respectively. The protocol violation codes were “concomitant medication”, “exclusion criteria”, “inclusion criteria”, and “study procedures/assessments” with 8, 5, 2, and 1 instances respectively.

The protocol violation codes with the greatest potential impact on study outcome were “Missing Endpoint Assessments”, “Study Treatment Administration/Dispense” and “Study Treatment Compliance” categories. The highest frequency in any code was “Study Treatment Admin/Dispense” in the 400mg treatment arm that was seen in 19 (17%) of patients. The greatest differential from placebo was seen in the “Study Treatment Compliance” code, in the 100mg treatment arm where there was a frequency of 15% compared to 8% in the placebo arm,

Table 9 .

Table 9 C017 Key Protocol Violation Codes by Frequency

Protocol violation Code*	Arm	Patient Count	% Patients
Missing Endpoint Assessments	PBO	4	4
	100mg	6	6
	200mg	3	3
	400mg	6	5
Study Treatment Admin/Dispense	PBO	13	12
	100mg	12	11
	200mg	16	15
	400mg	19	17
Study Treatment Compliance	PBO	8	8
	100mg	16	15
	200mg	12	11
	400mg	13	12

*all identified as "minor"

Reviewer Comment: Examination of each instance of the key protocol violation codes reveal a low likelihood of effect on study outcome because the distribution is balanced between treatment arms as in the "Missing Endpoint Assessments" code or the violations is not likely to have a consistent effect of seizure frequency, as in the "Study Treatment Admin/Dispense" code. The effect of the "Study Treatment Compliance" code is more likely to favor an increase in seizure frequency, therefore the distribution seen in this code would not bias the cenobamate treatment arms toward fewer seizures.

Table of Demographic Characteristics

There is no imbalance of demographic characteristics seen that is > 6% in large sample size. There is an underrepresentation of “BLACK OR AFRICAN AMERICAN” in the 400mg treatment arm. However, the n size of this group is small. This small size more readily allows a disproportion to occur, [Table 10](#).

Table 10 C017 Population Demographics

Distribution of Patients by Treatment Arm										
Actual Treatment for Period 01	Count	% of Total								
YKP3089 100 mg	108	24.80%								
YKP3089 200 mg	110	25.20%								
YKP3089 400 mg	112	25.70%								
Placebo	106	24.30%								
All	436	100.00%								
Age Distribution, n, Central Tendency										
Statistics	100mg	200mg	400mg	Placebo	Total					
N	108	110	112	106	436					
Mean	39.04	40.85	39.82	39.28	39.76					
Std Dev	12.06	12.4	10.56	12.17	11.79					
Min	19	19	21	19	19					
Quantiles25	29	31	33	29.75	31					
Median	37.5	40.5	38	38	38					
Quantiles75	49	49	48	48	48.75					
Max	66	69	66	70	70					
Age Strata by Treatment Arm										
Age Group	Count 100mg	% 100mg	Count 200mg	% 200mg	Count 400mg	% 400mg	Count Placebo	% Placebo	Count	% Total
Age 39 or younger	58	53.70%	54	49.10%	60	53.60%	61	57.50%	233	53.44%
Age between 40 and 64	48	44.40%	53	48.20%	50	44.60%	42	39.60%	193	44.27%
Age 65 and older	2	1.90%	3	2.70%	2	1.80%	3	2.80%	10	2.29%
All	108	100.00%	110	100.00%	112	100.00%	106	100.00%	436	100.00%
Sex Distribution by Treatment Arm										
	Count 100mg	% 100mg	Count 200mg	% 200mg	Count 400mg	% 400mg	Count Placebo	% Placebo	Count	% Total

F	51	47.20%	56	50.90%	59	52.70%	50	47.20%	216	49.54%
M	57	52.80%	54	49.10%	53	47.30%	56	52.80%	220	50.46%
All	108	100.00%	110	100.00%	112	100.00%	106	100.00%	436	100.00%
Racial Distribution by Treatment Arm										
	Count 100mg	% 100mg	Count 200mg	% 200mg	Count 400mg	% 400mg	Count Placebo	% Placebo	Count	% Total
ASIAN	10	9.30%	11	10.00%	11	9.80%	9	8.50%	41	9.40%
BLACK OR AFRICAN AMERICAN	4	3.70%	3	2.70%	1	0.90%	4	3.80%	12	2.75%
WHITE	89	82.40%	94	85.50%	97	86.60%	91	85.80%	371	85.09%
OTHER	5	4.60%	2	1.80%	3	2.70%	2	1.90%	12	2.75%
All	108	100.00%	110	100.00%	112	100.00%	106	100.00%	436	100.00%
Distribution of Ethnicity Group By Treatment Arm										
	Count 100mg	% 100mg	Count 200mg	% 200mg	Count 400mg	% 400mg	Count Placebo	% Placebo	Count	% Total
HISPANIC OR LATINO	8	7.40%	7	6.40%	13	11.60%	9	8.50%	37	8.49%
NOT HISPANIC OR LATINO	100	92.60%	103	93.60%	99	88.40%	97	91.50%	399	91.51%
All	108	100.00%	110	100.00%	112	100.00%	106	100.00%	436	100.00%
National Distribution by Treatment Arm										
	Count 100mg	% 100mg	Count 200mg	% 200mg	Count 400mg	% 400mg	Count Placebo	% Placebo	Count	% Total
USA	28	25.90%	28	25.50%	28	25.00%	26	24.50%	110	25.23%
POL	12	11.10%	12	10.90%	12	10.70%	12	11.30%	48	11.01%
BGR	9	8.30%	9	8.20%	10	8.90%	9	8.50%	37	8.49%
DEU	8	7.40%	9	8.20%	8	7.10%	8	7.50%	33	7.57%
KOR	8	7.40%	8	7.30%	8	7.10%	7	6.60%	31	7.11%
SRB	7	6.50%	7	6.40%	8	7.10%	6	5.70%	28	6.42%
ESP	7	6.50%	6	5.50%	7	6.30%	7	6.60%	27	6.19%
AUS	6	5.60%	6	5.50%	6	5.40%	6	5.70%	24	5.50%
CZE	6	5.60%	6	5.50%	6	5.40%	6	5.70%	24	5.50%
UKR	5	4.60%	6	5.50%	6	5.40%	6	5.70%	23	5.28%
HUN	3	2.80%	4	3.60%	4	3.60%	4	3.80%	15	3.44%
ISR	3	2.80%	3	2.70%	3	2.70%	3	2.80%	12	2.75%
GBR	2	1.90%	2	1.80%	2	1.80%	2	1.90%	8	1.83%
THA	2	1.90%	2	1.80%	2	1.80%	2	1.90%	8	1.83%
FRA	1	0.90%	1	0.90%	1	0.90%	1	0.90%	4	0.92%
ROU	1	0.90%	1	0.90%	1	0.90%	1	0.90%	4	0.92%

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The distribution of epilepsy characteristics is balanced across treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The C017 concomitant medication dataset does not have a dedicated variable for “reason”. Any instance of midazolam, diazepam or lorazepam is selected as a possible rescue medication. There were 12 instances identified containing one of these benzodiazepines. Four entries are eliminated because the concomitant medication end-of-treatment date was prior to the study treatment-start date. From the remaining 9 entries there were 9 patients where 2, 1, 2, and 2 patients had an entry for one of these benzodiazepines. The frequency of these exposures is balanced across the treatment arms and will not influence the study outcome.

Efficacy Results – Primary Endpoint

Table 11 presents the primary analysis of the percent change from baseline in seizure frequency per 28 days. All three YKP3089 dose groups were statistically significantly different from the placebo based on the rank ANCOVA model. The observed medians of percent change from baseline in seizure frequency per 28 days were -55.3%, -55.2%, -36.3%, and -24.3% for the YKP3089 400 mg/day group, YKP3089 200 mg/day group, YKP3089 100 mg/day group, and placebo group, respectively.

Table 11 Study C017, Efficacy Results, Primary Endpoint , mITT Population

Study 17 primary analysis, mITT population								
	YKP						Placebo	
Patient (n)	108		109		111		106	
	100mg		200mg		400mg			
	Actual	% Change From Baseline	Actual	% Change From Baseline	Actual	% Change From Baseline	Actual	% Change From Baseline
Baseline (n)	108		109		111		106	
Mean (SD)	21.9 (33.75)		30.6 (60.87)		24.1 (63.08)		25.8 (76.81)	
Median	9.5		11.0		9.0		8.4	
Min, max	3.5, 202		4, 418		4, 638		4, 759	
Endpoint (n)	108		109		111		106	
Mean (SD)	12.3 (20.68)	-33.6 (45.68)	22.4 (59.58)	-41.7 (50.59)	13.6 (43.86)	-48.3 (46.65)	21.6 (65.43)	-17 (50.26)
Median	5.8	-36.3	5.8	-55.2	3.8	-55.3	6.8	-24.3
Min, max	0, 164.6	-100, 205.6	0, 373.7	-100.0, 191.1	0, 424.9	-100.0, 166.7	0.7, 640.8	-90.6, 198.4
P value ^a	0.006		<0.001		<0.001			
^a p value is based on an analysis of covariance model with terms for ranked baseline seizure rate and randomized treatment group								
Includes seizure types of all simple partial motor, complex partial, or secondarily generalized seizures								

Data Quality and Integrity

Based on risk level assessment by OSI and concurrence by DNP two sites for clinical inspection were identified for study C017. Site 1010 was located in Philadelphia, PA where 9 patients were enrolled. Enrollment was distributed across the treatment arms as follows; there were 2,1,4, and 2 patients enrolled in the placebo, 100mg, 200mg, and 400mg arms respectively. There was 1 screen failure identified. The second site selected was number 1016 located in Baltimore MD. There were 19 patients enrolled. Enrollment was distributed across the treatment arms as follows; there were 2, 4, 5, and 8 patients enrolled in the placebo, 100mg, 200mg, and 400mg arms respectively. There was 1 patient not assigned to treatment and 2 screen failures at the site. There was also an FDA Establishment Inspection of the sponsor for study C017.

The CIS overall findings (for both studies C013 & C017) noted inspectional observations at one of the clinical investigator sites (C017), as well as at the sponsor and CRO, these findings are unlikely to have a significant impact on overall study results. OSI concluded that the study data generated are considered acceptable and may be used in support of this NDA.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy analysis also demonstrated a significant number of responders ($\geq 50\%$ reduction from baseline in seizure frequency) with an ascending dose response from the 100mg to the 400mg treatment arm over the placebo group, [Table 12](#).

Table 12 C017, Efficacy Results, Secondary Endpoint- Responder Rate

	Cenobamate (YKP)						placebo	
	100mg (n=108)		200mg (n=109)		400mg (n=111)		N	%
Responder	N	%	N	%	N	%	N	%
Yes	44	40.7	63	57.8	67	60.4	23	21.7
No	64	59.3	46	42.2	44	39.6	83	78.3
P value	0.003		<0.001		<0.001			
P values are based on Fisher's chi-square exact test. A step-down procedure is used to interpret the results to ensure the overall type I error rate is controlled at the 5% level. The hierarchy for comparisons is YKP3089 200 mg vs placebo, YKP3089 400 mg vs placebo, YKP3089 100 mg vs placebo.								

Dose/Dose Response

See Section [7.1.4 Dose and Dose-Response](#)

Durability of Response

See Section [7.1.5, Onset, Duration, and Durability of Efficacy Effects](#)

Persistence of Effect

See Section 7.1.5, [Onset, Duration, and Durability of Efficacy Effects](#)

Additional Analyses Conducted on the Individual Trial

none

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Two individual Studies C013 and C017 were not pooled

7.1.1. Primary Endpoints

See Section 6

7.1.2. Secondary and Other Endpoints

See Section 6

7.1.3. Subpopulations

See Section 6

7.1.4. Dose and Dose-Response

In study C013 the sponsor's strategy for assessing dose response was examination of seizure frequency by dose during titration phase of the study. A moving average of seizure frequency by study visits, that represent dose epochs, was created. This analysis reveals declining seizure frequency as treatment progresses from titration through the 200mg treatment target. The sponsor does not provide corresponding cenobamate concentrations to provide assessment of concentration response. This analysis is shown in [Table 13](#).

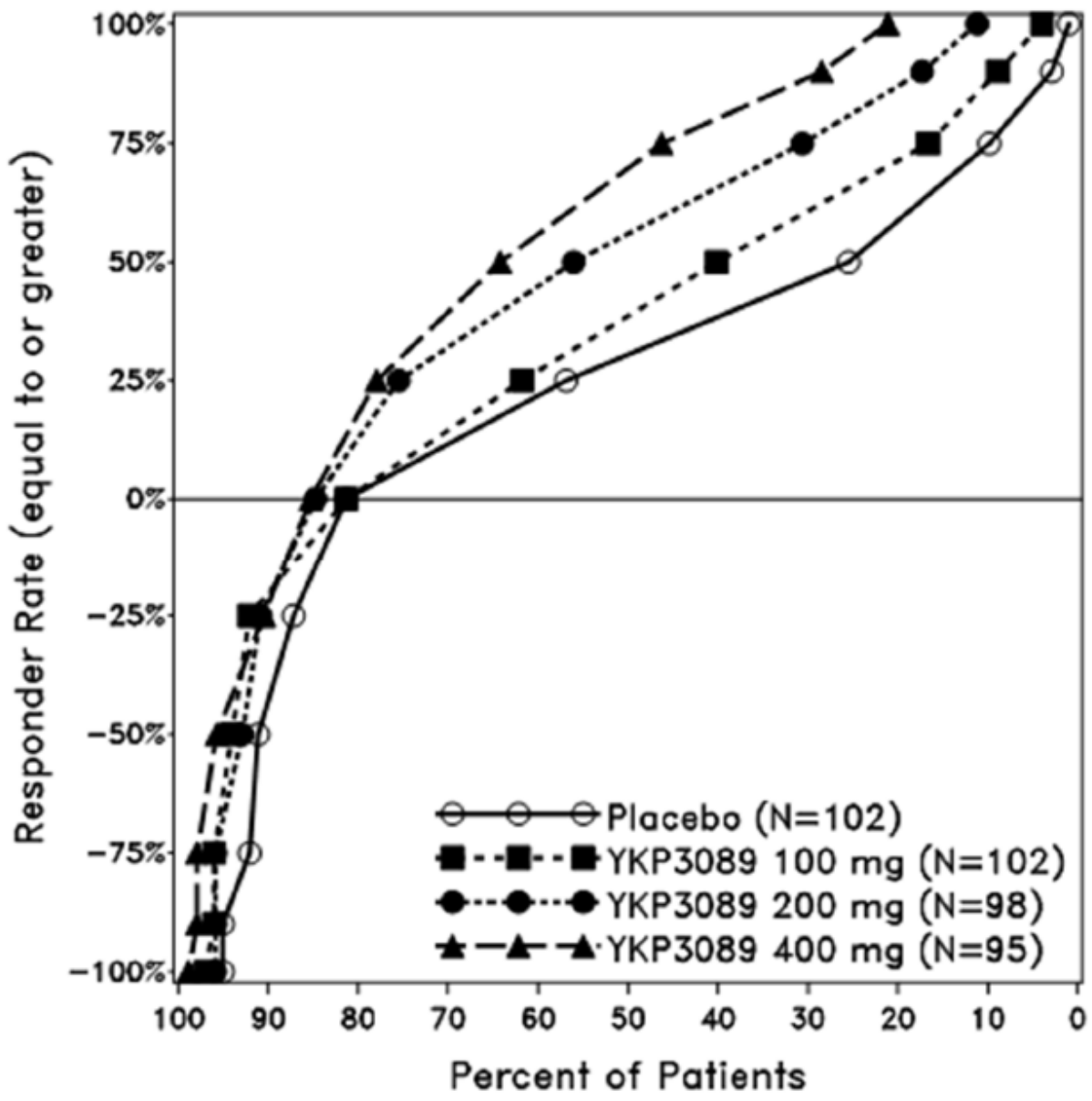
Table 13 Dose Response Analysis: Frequency per 28 Days Moving Average Using 4-Week Intervals During Double-Blind Treatment Period – Completer Population (from C013 CSR, Table 9, page 68)

Visit Intervals	YKP (n=102)		Placebo (n=99)	
	Actual frequency / 28 days	% Change from Baseline	Actual frequency/ 28 days	% change from baseline
Baseline	7.7		5.5	
Visit 3-7	4.2	40.6	5.0	14.3
Visit 5-9	4.0	44.7	6.0	17.0

Visit Intervals	YKP (n=102)		Placebo (n=99)	
	Actual frequency / 28 days	% Change from Baseline	Actual frequency/ 28 days	% change from baseline
Visit 7-10	3.0	56.1	5.0	15.8
Visit 9-11	3.0	62.8	4.2	32.2
Visit 10-12	3.1	63.5	4.2	36.2
Note: Baseline Seizure Frequency per 28 Days = Number of seizures over baseline period (56 days prior to Study Day 1) divided by the number of days in the interval multiplied by 28				
Note: Each 4-week Interval Frequency = Number of seizures over entire the 4-weeks divided by the number of days in the interval multiplied by 28.				

In the study C017 Clinical Study Report, the sponsor’s strategy for assessing dose response was examination of responder rate by dose group, [Figure 6](#). This analysis reveals a maximum difference between treatment arms at the 50% responder rate. At this responder rate the approximate proportion of patients that achieve this rate are 25%, 40%, 55%, and 65% in the placebo, 100mg, 200mg, and 400mg treatment arms respectively.

Figure 6 Cumulative Distribution of Responder Rate by Treatment Group (MITT-M Population)
(from C017 CSR, Figure 6-3, page 128)

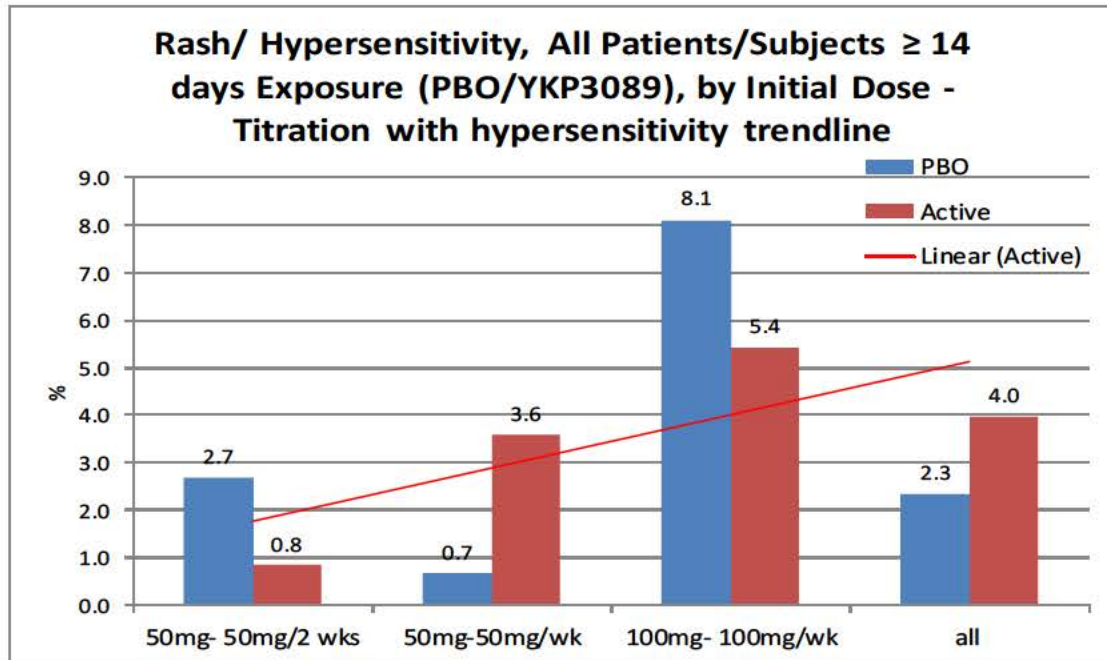


To see the FDA assessment of dose response, refer to the OCP dose response presentations in Section 4.5.2, [Dose Response](#).

Dose response is of interest in this application because the titration rate in study C013 and C017 had a more rapid escalation of cenobamate dose than in proposed labeling, [Figure 8](#). This issue emerged due to the DRESS risk seen in phase 1 and pivotal studies. Hypersensitivity reactions were seen to be fewer when dose escalation was slower, see [Figure 7](#). Based on these observations and the potential for immune tolerance discussed in [Section 8.6.1, DRESS Risk](#). The

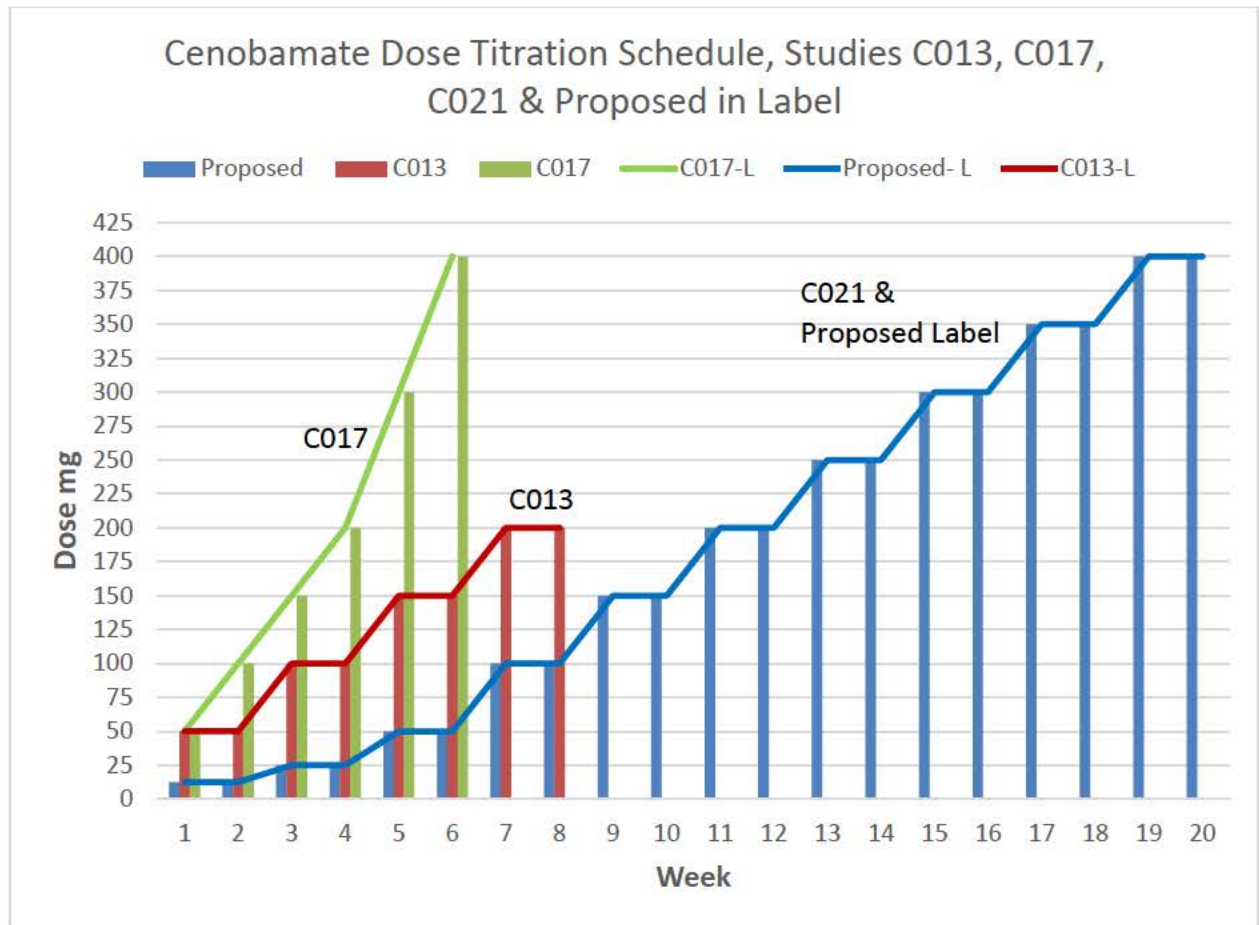
resulting strategy to reduce DRESS risk was a reduction of the rate of dose escalation in study C021. There were no further DRESS case identified in this study (n=1344). This dosing strategy is carried into proposed labeling.

Figure 7 Hypersensitivity Case Frequency Trend Related to Titration Rate



The cenobamate titration schedule in study C021, slowed in escalation compared to the pivotal studies, is the benchmark that has been established for DRESS reduction. The benefit of accelerating dose escalation to achieve more rapid seizure reduction (increased rate of rise to therapeutic concentration) need to be balanced against the potential of an increase in DRESS risk. The increase in DRESS risk between the pivotal study titration rates and the rate in C021 has not been established and cannot be predicted. The OCP estimate (Section 4.5.2, Dose Response) reveals that half the maximal benefit is reached at week 5 and the benefit of 100mg is achieved at approximately 7 weeks (based on median % change from baseline in study C017). This duration of titration to therapeutic effect is acceptable and does not support alteration of the proposed schedule.

Figure 8 Cenobamate Dose-Titration Schedule by Study Compared to Proposed Labeling, C013, C017 and C021



7.1.5. Onset, Duration, and Durability of Efficacy Effects

The OCP reviewer examined the percent change from baseline of monthly seizure frequency in study C013 and C017, see [Figure 2](#) and [Figure 3](#). In study C013 the last titration epoch and one maintenance epoch are compared, the first-time interval was day 29 to 57 (titration) while the second was day 57 to 85 (maintenance). There was no noticeable change in frequency across these two epochs. The span of epochs from C013 was short. A longer span is available in study C017 where three maintenance epochs are available for inspection. The three maintenance epochs span weeks 6-10, 10 to 14 and 14 to 18 respectively. There is a small loss of seizure reduction between the first and second maintenance epoch but no change between maintenance epoch 2 and 3. That second interval covers weeks 10 to 18 without notable decline in efficacy.

Study C012 did not have quantitative seizure diary data for examination. The frequency of epilepsy related adverse events was examined to assess seizure worsening, see [Seizure Worsening Analysis](#). This may act as a proxy for durability of efficacy. If there were more frequent seizure breakthrough as the 1-year study timeline progressed, that would be an indicator of loss of efficacy effect. The examination showed a rate of epilepsy / seizure adverse events consistent with background sporadic breakthrough but no upward trend that would be a signal for loss of effect.

Reviewer Comment: the available analyses support an acceptable durability of cenobamate treatment effect.

7.1.6. Considerations on Benefit in the Postmarket Setting

Benefit in the post marketing setting will likely reflect the inclusion criteria of patients that have failed one or more AEDs.

7.1.7. Other Relevant Benefits

The primary indication reflects the expected benefit

7.2. Integrated Assessment of Effectiveness

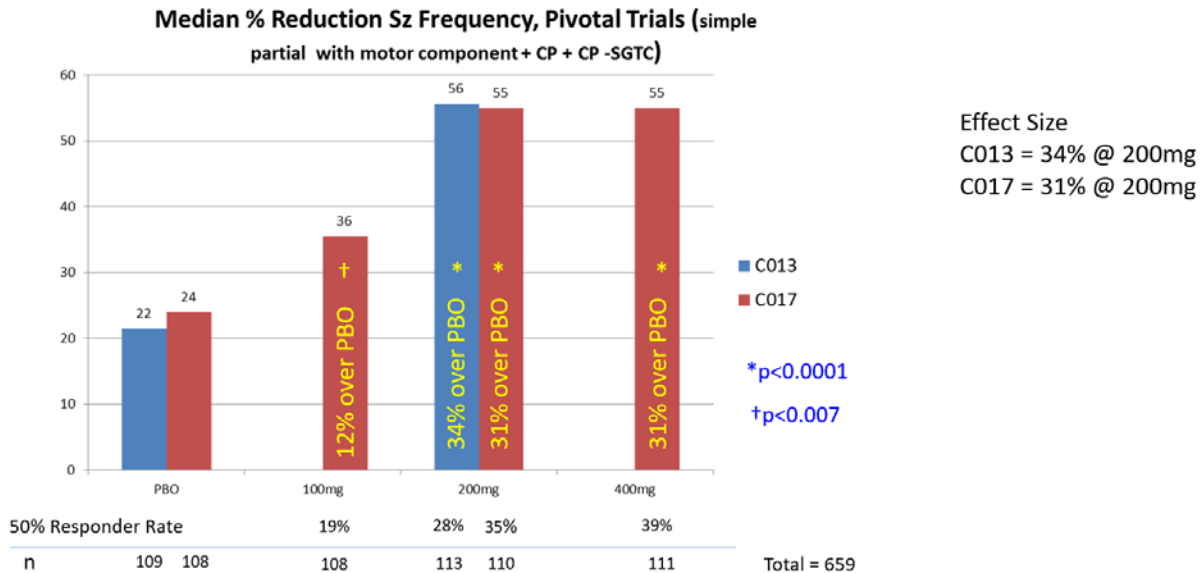
The biometrics reviewer has a comment on study C013 regarding the execution of the interim analysis but overall found the results acceptable in the context of the results of both studies C103 and C017. The biometrics reviewer in examination of the collective evidence also concluded that cenobamate is effective for the treatment of partial seizures.⁶ A summary graphic of the pivotal study results is shown in [Figure 9](#).

⁶ Division of Biometrics 1, Statistical Review and Evaluation, NDA 212839, 7/29/19

Figure 9 Summary of Cross Study Efficacy Results, C013 & C017

Pivotal Trial Results, C013, C017

- C013 ITT Population : all patients with 1 efficacy evaluation
- C017 MITT population: all patients who received a single dose of study medication



8. Review of Safety

8.1. Safety Review Approach

8.1.1. Overview

Although there are three open US INDs for YKP3089, epilepsy (IND 76,809) is currently the only indication being studied (DSUR- 10/2018). The first study of YKP3089 was initiated as IND (b) (4) on 8/12/05 (b) (4)

At the time of the submission of IND 76809 approximately 100 patients had been exposed to YKP3089 in two studies: one completed single dose sequential administration study that examined doses of 5 to 750 mg, and a second 14-day multiple dosing (QD) study which provided preliminary data on patients receiving 50 and 150 mg QD. No serious adverse events were reported in these studies. One patient was withdrawn from the multiple dosing study for reasons of blurred vision associated with headache and dizziness; this was later thought to be consistent with migraine. In summary, there were no notable worrisome signals from the clinical trials that preceded the opening of IND 76809 (indication epilepsy).

Reexamination, by this division, of preclinical data at the time of review at the opening of IND 76809 revealed an underlying event in monkeys that is worrisome in the population of patients with epilepsy. Two studies demonstrated seizures in monkeys associated with the administration of YKP3089. In one study a seizure occurred following the second YKP3089 dose of 60mg/kg. In another study consisting of 2 monkeys receiving 60mg/kg/day both had seizures on the second day of administration. After lowering the dose to 40mg/kg/day, no seizures were observed.

The Sponsor failed to adequately explain the findings of seizures in monkeys. The Sponsor did revise the protocol in a fashion, as recommended, by the division to allow individual patients to be tested with lower doses before exposure to higher doses. They also altered the study so that the initial lower dose of exposure and the maximal dose is reduced. The lower proposed dose appeared to have an adequate safety margin while the proposed upper dose remained more than the required safety threshold. The division had a teleconference with the Sponsor on 4/25/07 at which time they were told that they may proceed with the protocol provided the single dose did not exceed 250 mg. At the most conservative, considering underestimation of the margin based upon single dose PK in monkeys, this would result in a 7-fold safety margin for C_{max} and a 3-fold safety margin for AUC. Because of the rather long half-life this compound the Sponsor was also: 1) asked to expand the short visits from 24 to 48 hours and 2) allow at least 2-week washout after these short clinical visits.⁷

On December 17, 2010 there was a meeting Type B where the sponsor presented questions on the design of study C013 with a maximum dose was 200mg. Enrollment in study C017 was started on 7/31/13 with a placebo, 100mg, 200mg and 400mg dose arm.

An initial safety report on subject (b) (6) was submitted by the sponsor on June 26, 2015. The subject was a 38 yo female, healthy volunteer, in study YKP3089C020 a TQT study. The patient received 32 days of treatment with YKP3089. Study drug was discontinued but signs and symptoms of DRESS syndrome progressed. The subject subsequently expired 54 days after study drug was discontinued. Cause of death determined at autopsy was “determined to be cardiac dysrhythmia due to eosinophilic myocarditis due to adverse reaction to experimental drug”. Two additional reports of DRESS syndrome were also reported in the initial submission on subject (b) (6). These subjects recovered without sequelae. Following this event, a partial clinical hold was imposed in 11/9/2015 for patients treated with YKP3089 for less than 4 months and any healthy volunteers in clinical studies and new patient enrollment into ongoing studies. Patients who were on YKP3089 treatment for 4 months or longer were permitted to continue treatment. Complete discussion of the DRESS safety issue and sequence of clinical hold and the approach to resolution of safety concerns is presented in Section 8.6.1, [DRESS Risk](#).

Review of safety is directed at the indication of partial onset seizures in adults. There is a focus on the potential for DRESS a hypersensitivity reactions with a dedicated safety review of study

⁷ Norman Hershkowitz MD, PhD Medical Review, Complete Response to Hold, 6/15/07.

C021 to assess the DRESS issue. Following the emergence of this safety signal in the phase 1 and 2 stages of development a larger, open label, safety study, C021 was performed to investigate the frequency of DRESS with a reduced titration schedule. Two, pivotal studies, C013 and C017 provide placebo-controlled safety data. In addition, due to the nonclinical signal of seizure occurrence in monkeys, an examination for the detection of seizure worsening is performed, see Section 8.4.5, [Seizure Worsening Analysis](#).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

C013-C017 DB & OLE Study Cenobamate Exposure

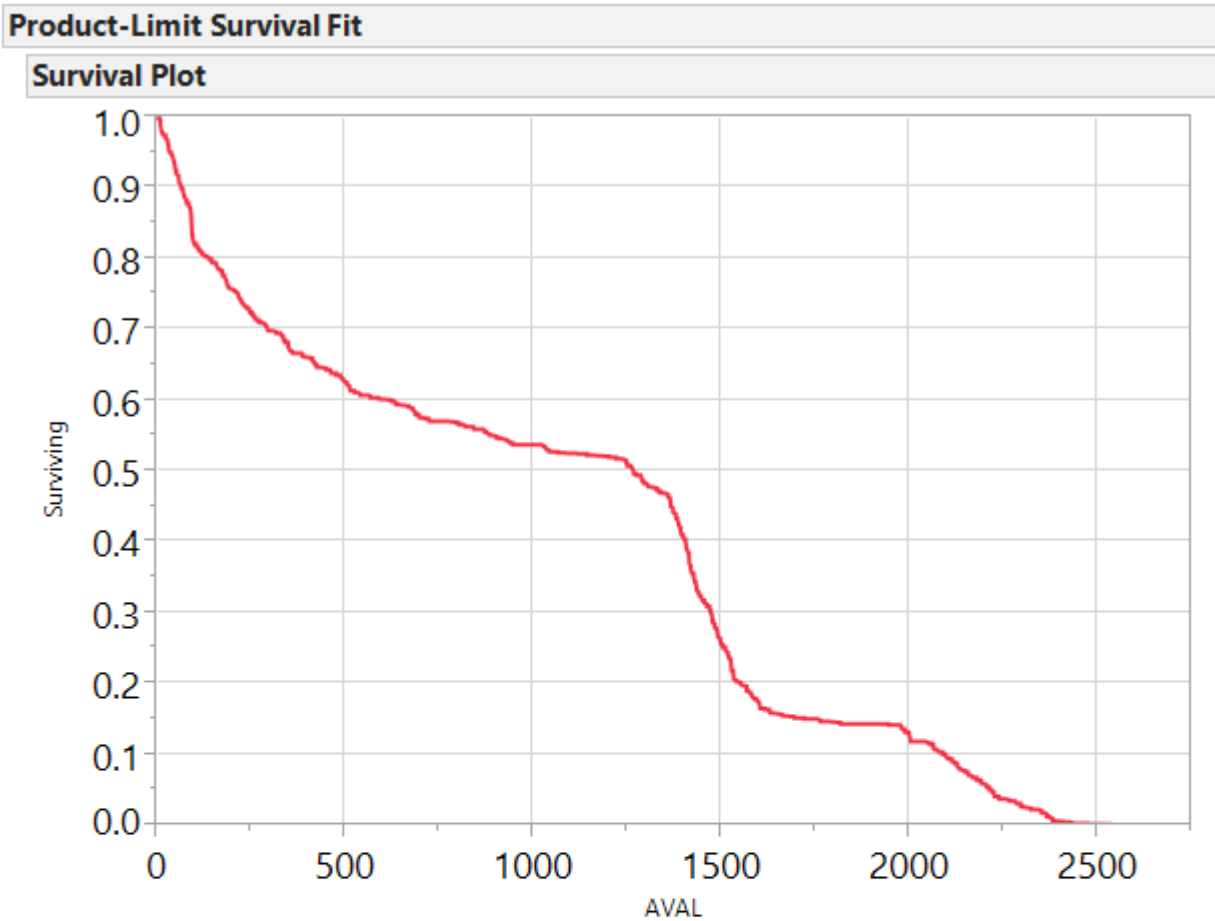
The Phase 2/3 patient datasets are grouped as where studies C013 & study C017 both double blind (DB) and open label extension (OLE) are one group and the second is study C021.

The mean, median and maximum number of exposure days in the 605-patient group are shown in [Table 14](#). A Kaplan–Meier Plot of the proportion of patients remaining in the study by study day provides a visual image of the flow of patient retention / attrition in the two studies (pool) over time, [Figure 10](#). The distribution of mean dose by frequency of patients at that mean is shown in [Figure 11](#). The frequency of modal dose is shown in [Table 15](#) where the two most frequent modes are 200mg and 300mg occurring in 167 and 136 patients respectively.

Table 14 C013-C017 DB & OLE, Mean, Median and Maximum Days of Cenobamate Treatment

Days of Exposure in Studies C013-C017, DB-OLE			
# Patients	Mean of Days / years on Treatment	Median of days/ years on treatment	Maximum # Days / years on Treatment
605	1001	1265	2576
	2.7	3.5	7.1

Figure 10 Kaplan–Meier Plot, Proportion of Study C013-C017 DB-OLE Patients on Treatment by Number of Study Days, Mean and Quantiles (n=605)



Time to event: AVAL
 Censored by AVAL
 Censor Code 1

Summary

Group	Number failed	Number censored	Mean	Std Error
Combined	604	1	1003.03	30.3362

Quantiles

Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
Combined	1265.5	939	1363	215	1510

Figure 11 C013-C017 CB-OLE, Mean Dose by Patient Count During Cenobamate Treatment Period

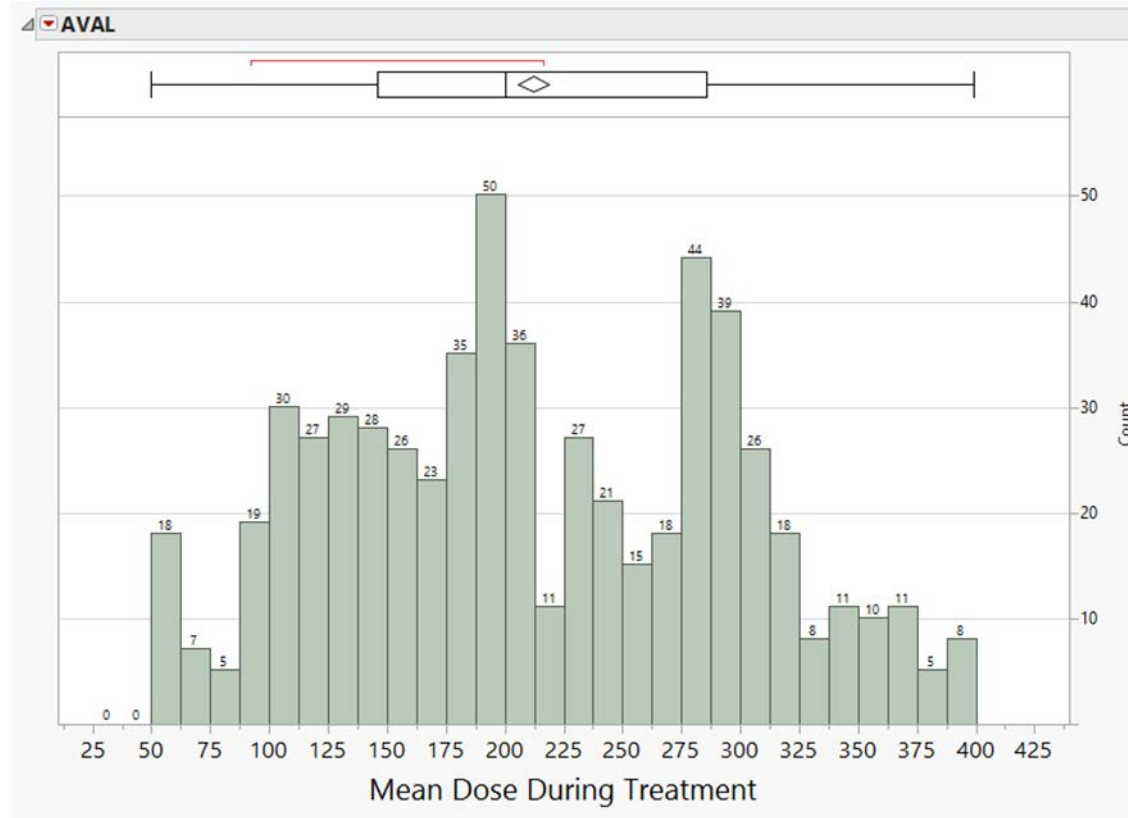


Table 15 C013-C017 DB & OLE, Modal Dose by Patients Frequency (n= 605)

Mode Value	# Patients
50	29
100	91
150	62
200	167
250	26
300	136
325	1
350	25
400	68

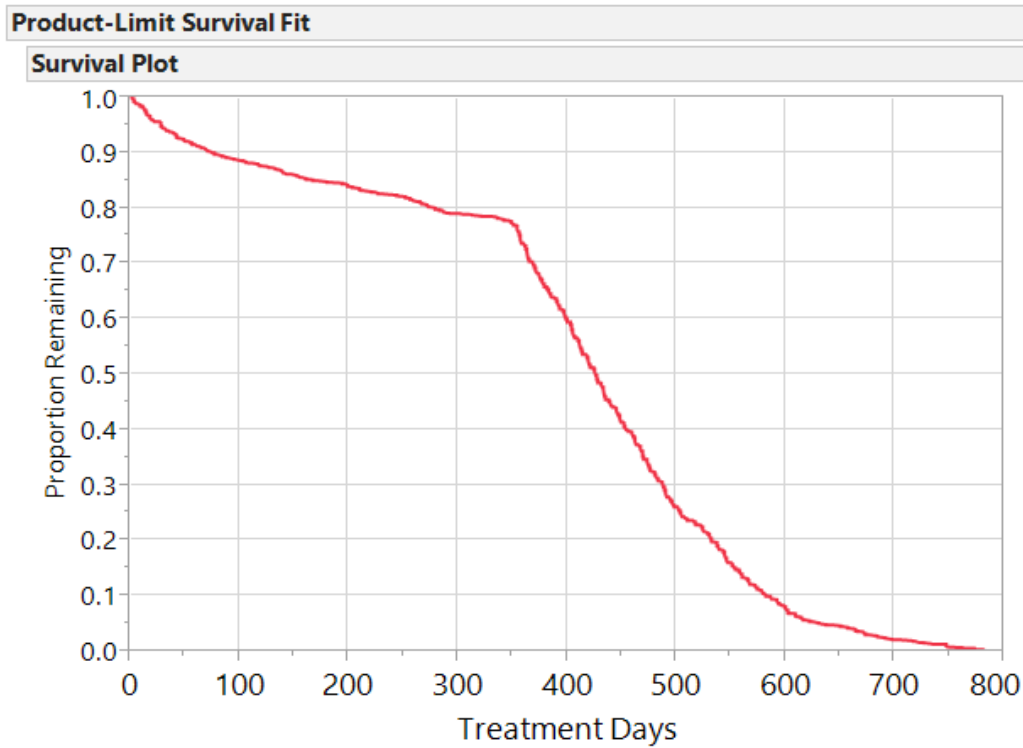
Study C021

The mean and median of total study days of treatment for all study C021 patients were 398 and 426 days respectively, shown in [Table 16](#) while a Kaplan–Meier Plot is used to show the proportion of patients remaining in study C021 by study day in [Figure 12](#).

Table 16 C021, Mean and Median of Total Days in Study from All Patients

# Patients	Mean # Days	Median # Days
1340	398	426

Figure 12 C021, Kaplan–Meier Plot, Proportion of Study Patients on Treatment by Number of Study Days, Mean and Quantiles (n=1340)



Time to event: AVAL

Censored by AVAL

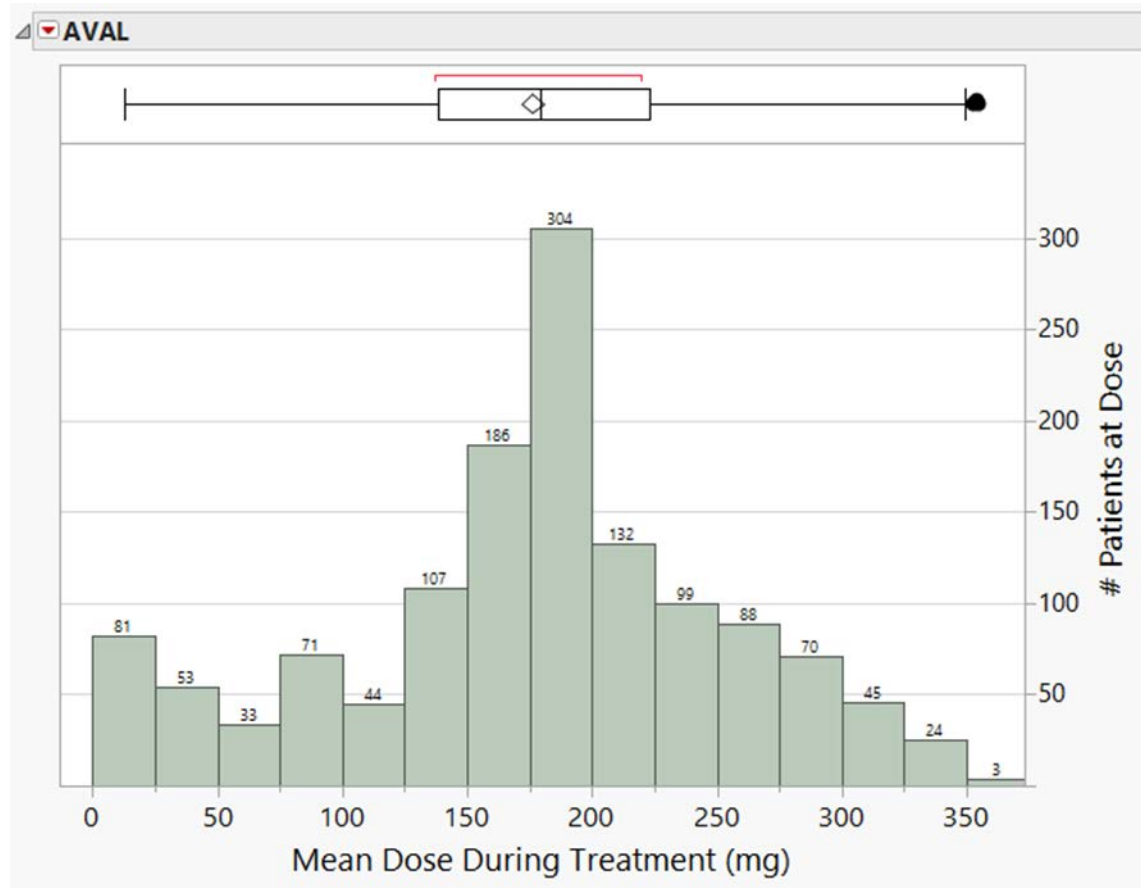
Censor Code 1

Summary				
Group	Number failed	Number censored	Mean	Std Error
Combined	1338	2	398.257	4.76701

Quantiles					
Group	Median Time	Lower 95%	Upper 95%	25% Failures	75% Failures
Combined	426	419	433	357	504

The distribution of mean patient dose while on cenobamate treatment in study C021 is shown in [Figure 13](#). The most frequent mean dose was in the range from 175 to 200mg of cenobamate taken by 304 patients.

Figure 13 C021, Mean Dose by Patient Count During Cenobamate Treatment (n=1340)



The distribution of modal dose across the patients participating in study C021 is shown in [Table 17](#). The most frequent mode is 200mg where 498 patients were in the group. The top three modal dose points were 200mg, 250mg, and 300mg corresponding to 498 patients, 153 patients, and 147 patients respectively.

Table 17 C021, Distribution of Modal Dose by Patient Frequency (n= 1340)

Study C021	
Modal Dose	# Patients
12.5	78
25	28
50	45
75	1
100	108
125	1
150	116
200	498
250	153
300	147
350	74
400	91

Phase 2/3 Safety Dataset Pool

Modal dose in the safety dataset had a peak at 200mg for 710 patients. There were 288 patients and 127 patients with a modal dose of 300mg and 400mg respectively, [Table 18](#).

Table 18 Safety Dataset Exposure Duration and Modal Dose, C013-C017 POOL & C021

C013-C017 Pool, C021, ISS (n=1944)	
Duration, months	# Patients
6 months	865
12 months	710
Modal Dose, mg	
12.5	78
25	28
50	77
100	201
150	176
200	710
250	166
300	288
350	89
400	127

Reviewer Comment:

Overall exposure was adequate. The sum of exposure in the pivotal studies with open label extensions and study C021 met the ICH E1A guidelines. There were 865 patients with exposure to cenobamate for at least 6 months and 710 patient for at least one year, see [Table 18](#). Examination of the study C013-C017 pool reveals that approximately half of patients maintained cenobamate treatment for 1000 days. A high proportion of patients achieved a mean dose in the recommended dose range. Examination of study C021 reveals approximately half of patients maintained cenobamate treatment for 400 days. A high proportion of patient achieved a mean dose near the recommended dose range while the majority of patients had a modal dose at or above the recommended dose of 200mg. This comprehensive evaluation reveals sufficient exposure to adequately support proposed dosing and is also sufficient to support the safety review.

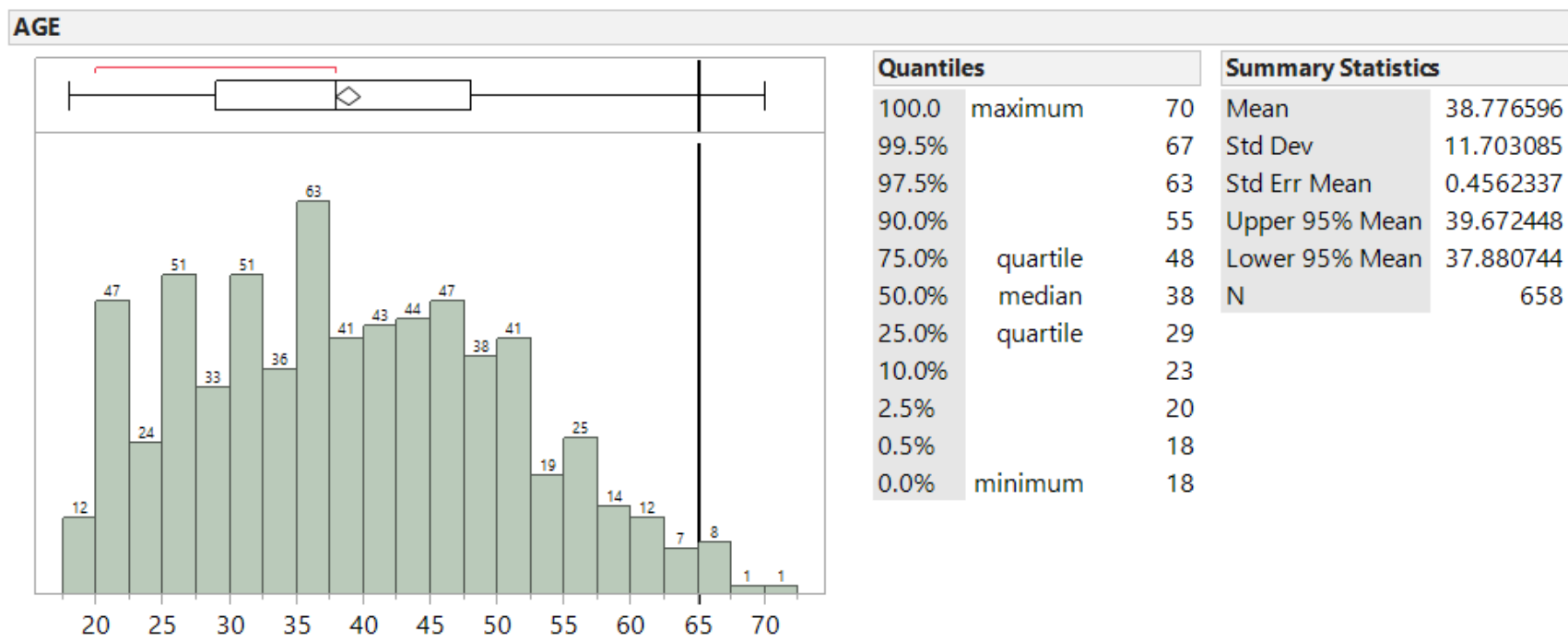
8.2.2. Relevant characteristics of the safety population:

Pool C013-C017

Table 19 C013-C017 Pool, Distribution of Study Population by Sex, Race and Ethnicity

SEX	# patients	% Patients
F	325	49
M	333	51
RACE	# patients	% Patients
WHITE	486	74
ASIAN	135	21
BLACK OR AFRICAN AMERICAN	17	3
OTHER	15	2
UNKNOWN	5	1
ETHNIC	# patients	% Patients
HISPANIC OR LATINO	44	7
NOT HISPANIC OR LATINO	605	92
NOT REPORTED	9	1
NOT REPORTED	9	1

Figure 14 C013-C017 Pool, Distribution of Patient Age, Mean 38.7 years



Reviewer Comment: The pivotal study pool is balance by Sex. Median age is 38 years. Racial balance is predominantly “white” with a moderate size subset of “Asian” participants. The “HISPANIC OR LATINO” and “BLACK OR AFRICAN AMERICAN” are underrepresented relative to the general US population, [Table 19](#), [Figure 14](#).

Study C021

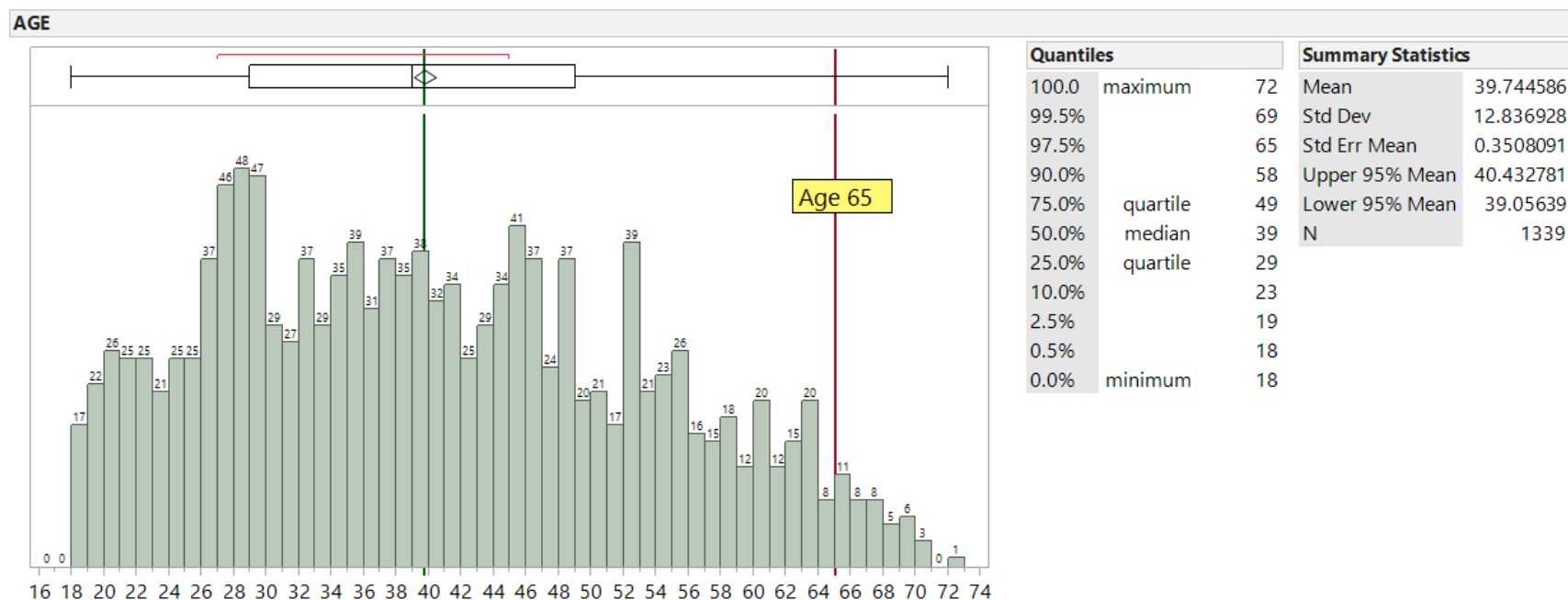
Examination of the study C021 ADSL dataset reveals an equal proportion of males and females. Racial distribution is predominantly “white” with all other groups representing 7 percent or less. The next largest defined group is “Asian” representing 5% of the patient population, [Table 20](#). [Table 20 C021, Distribution of Study Population by](#)

Table 20 C021, Distribution of Study Population by Sex, Race and Ethnic Group

SEX	# Patients	% Patients
F	666	50
M	673	50
RACE		
WHITE	1063	79
OTHER	91	7
ASIAN	73	5
AMERICAN INDIAN OR ALASKA NATIVE	59	4
BLACK OR AFRICAN AMERICAN	47	4
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	6	0
Ethnicity		
HISPANIC OR LATINO	282	21
NOT HISPANIC OR LATINO	1057	79

Age distribution is examined and reveals a mean and median age in the safety dataset of 39.7 and 39 respectively. There were 31 patients ≥ 65 years, see [Figure 15](#).

Figure 15 C021, Distribution of Patient Age



Reviewer Comment: the population in study C021 is balanced by sex and age. 80% of participants are “white” with 21% “HISPANIC OR LATINO”. The “BLACK OR AFRICAN AMERICAN” group is under represented relative to the general US population.

Reviewer Comment, Demographics

The safety database is balanced by Sex and has an age distribution commonly seen in partial onset seizure studies. The racial mix is predominantly “white” with a “BLACK OR AFRICAN AMERICAN” and that is no in alignment with the general US population.

8.2.3. Adequacy of the safety database:

The clinical safety database provides adequate patient exposure by sample size and dose, to assess cenobamate safety.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The narrative clinical study reports for both phase 1, study C013 and C017 were complete. The xpt datasets, that were the primary support for assessment and analysis in this review were complete.

8.3.2. Categorization of Adverse Events

There were no systematic lumping or splitting of adverse events detected. The adverse events datasets were Re-formatted for use with the ODE I Query Coding.

8.3.3. Routine Clinical Tests

Clinical chemistry, hematologic and urinalysis panels obtained during the phase 1, pivotal studies and study C021 were adequately complete.

8.4. Safety Results

8.4.1. Deaths

There were 16 deaths in the Cenobamate development program, [Table 21](#). A visual summary of the dose, timeline, category and cause of deaths in the development program is shown in [Figure 16](#).

One death occurred in the baseline period leaving 15 deaths that occurred during Cenobamate treatment. There were no deaths during the double-blind treatment period. There were 10 deaths during the open label extension period of studies C013 and C017 and 4 deaths during open label study C021. One death due to DRESS occurred during a phase 1 thorough QT study.

The death with the most serious implications during the development program occurred in a healthy volunteer patient in the TQT study. The patient developed DRESS syndrome after 32 days of treatment with YKP3089 at a dose of 200mg a day during days 22 to 32 of treatment. The disease process progressed after cessation of study drug although there was partial improvement with prednisone treatment. Prednisone was discontinued on day 64 followed by

an increase in eosinophils and death 51 days after cessation of study drug on day 84. The issue of DRESS is discussed more fully in [section 8.5.1, DRESS Risk](#).

There were three cases of cardiogenic death. The first (patient (b) (6) study C013 OLE), due to unexplained cardiac arrest where a 58-year-old patient had right sided chest pain followed by diaphoresis and collapse. The subject subsequently went into irreversible cardiac arrest. In the second case a 60 yo female (patient (b) (6), C017 OLE) with a prior history of a “cardiovascular accident” developed “stomach pain” and within minutes collapsed and became unresponsive. In the third case a 39 yo male (patient (b) (6) study C017 OLE) developed unexplained cardiogenic shock. This patient had a prior adverse event of “dyslipidemia” although no history of coronary artery disease is reported. In cases 1 and 3 the causal relationship to cenobamate is not supported by the long latency to the event. In both of these cases the cardiogenic event occurred after approximately 2 years of treatment. In the second case (patient (b) (6) C017 OLE) the myocardial infarction occurred after 300 days of cenobamate treatment. In this case there was evidence of pre-existing cardiovascular disease, listed as “cardiovascular accident”.

There were 3 cases of SUDEP, 1 each after 282, 200 and 129 days of treatment. Based on a conservative estimate of overall exposure to Cenobamate the SUDEP rate in the development program is 3.1/1000 patient years. This is comparable to a rate of 4.2/1000 patient in refractory epilepsy patients reported in 2016.⁸

There was one case, in a 60 yo male (patient (b) (6) study C021) of death due to traumatic intracranial hemorrhage acquired during a seizure. The head injury due to seizure was the second experienced by this patient during cenobamate treatment. This may be a case of drug ineffective. Potential for seizure worsening will be further explored in [Section 8.4.5 Seizure Worsening Analysis](#)

There were two cases of completed suicide, the 1st (patient (b) (6) study C013 OLE) after 132 days of cenobamate treatment and the 2nd (patient (b) (6) study C017 OLE) after 3.8 years of treatment. Causality is not well supported in the second case due to the absence of temporal relationship to treatment initiation. In the 1st case the 4-month latency allows for causality. Suicide risk is a known class effect of Antiepilepsy medications, the single case with possible temporal relationship does not define a change in this safety risk.

There were 2 deaths related to physical trauma in pedestrians in traffic collisions. There was one case in a 57 yo male (patient (b) (6) study C017 OLE) reported to have sepsis from a complication of pneumonia. There is no report of seizure with a related aspiration. A severely medically compromised 21 yo female (patient (b) (6) study C021) with Angelman syndrome developed urosepsis with a prolonged hospital course and respiratory failure. A decision was made to withdrawal life support. In the final fatal case, a 41 yo female (patient (b) (6), study

⁸ Devinsky O, et. al, Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016; 15: 1075–88. PMID: 27571159 DOI: 10.1016/S1474-4422(16)30158-2

Clinical Review
Steven Dinsmore, DO
NDA 212839 (cenobamate) XCOPRI

C017 OLE) had a seizure with aspiration and hypoxia. The patient called EMT but was subsequently found unresponsive at home. There was a hospital course consistent with multiorgan failure and hypoxic encephalopathy from the initial hypoxic event.

Table 21 Deaths During YKP3089 Development Program

Subject ID	Study Number	PT term(s)	Dose	Study day	History	Comment
(b) (6)	YKP3089C013 DB	SUDEP			Baseline	Unassociated, occurred during baseline
(b) (6)	YKP3089C013 OLE	SUDEP	200	267	27 yo F, VNS, Rx Trileptal, Potiga, Agree- SUDEP. The subject's medical history was significant for left hip dysplasia at birth, club feet, brain stimulator (Sante clinical trial from (b) (6) to (b) (6)), vagal nerve stimulator implantation (b) (6) left hip reduction (b) (6) plastic surgery to finge (b) (6) intermittent hand tremors (since (b) (6)) and memory impairment (since (b) (6)). On (b) (6) the subjects father reported an overall improvement in seizure frequency. On the morning of (b) (6), the subject's father found her face down in her pillow in bed without breathing and without pulse. An ambulance was summoned but efforts to resuscitate the subject were unsuccessful.	SUDEP, uncertain relationship
(b) (6)	YKP3089C013 OLE	cardiac arrest	200	697	58 Yo M, brain tumor resection, VNS, CBZ, TPM. R Chest pain, diaphoresis- collapse to cardiac arrest, risk profile unknown. While at home, the subject complained of right-sided chest pain radiating to his back and pain in his legs. He began to sweat profusely and fell to the bottom of the stairs with no loss of consciousness. His wife called the ambulance. Upon arrival, the medics witnessed the subject go into cardiac arrest and advanced life support measures were initiated. He was transported to the emergency room but did not respond to treatment. DAY 697	cardiac arrest, relationship to cenobamate uncertain for this event that occurred after 1.9 years of treatment. No cardiac risk history noted. Patient had extensive brain surgery with tumor resection in 1979, right temporal resection in 2008 and brain hematoma resection in 1978.
(b) (6)	YKP3089C013 OLE	completed suicide	100	132	42 yo M, 50mg during DB, increased to 100mg, (b) (6) taper due to AE (breakthrough Sz) began (b) (6) anger and aggression at office. Abdominal stab wounds thought to be suicide, Day 132, 46 days after entering open label treatment.	completed suicide is a potential class effect.
(b) (6)	YKP3089C017 OLE	myocardial infarction	300	1143	60-year-old white female, concomitant lacosamide, zonisamide, lorazepam, on 300mg YKP on day 1142 of MI event. On (b) (6) (Day 1142), the subject experienced a severe SAE of myocardial infarction. According to the CIOMS report, the subject was watching television when she began to complain of stomach pain. Within minutes, the subject fell from	myocardial infarction after 3.1 years of treatment causal relationship not supported by temporal relationship, more likely associated with prior history of "cardiovascular accident."

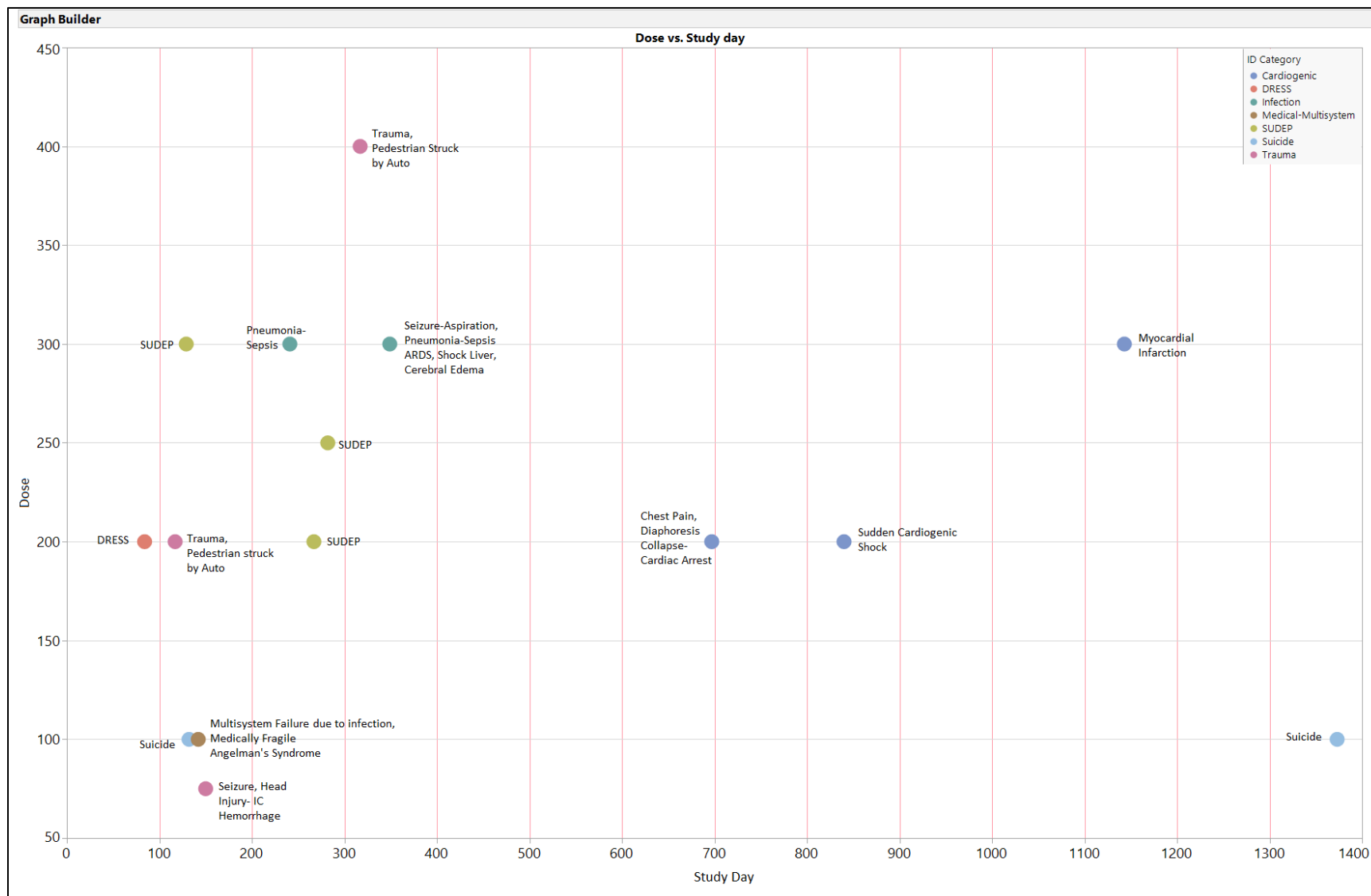
Subject ID	Study Number	PT term(s)	Dose	Study day	History	Comment
					her chair, collapsed, and became unresponsive. // Medical history included autoimmune thrombocytopenia; cardiovascular accident; hyponatremia; postmenopausal; ear drum surgery; nasal polyps; chronic ear drum infection in the left ear and having trouble hearing; ear infections; fracture of L1 and L3; fractured right wrist; fracture of right clavicle; fracture of left clavicle; right rib 3, 4, 5 fracture; concussion; left breast mastectomy; psychotic disorder; chronic sinus infection; sleep apnea; chronic upper respiratory infection; dermatofibroma; multiple cysts on arms, legs, and trunk of body; and burns on bilateral arms.	
(b) (6)	YKP3089C017 OLE	sepsis	300	349	41 yo F, pt had seizure and aspiration with subsequent aspiration pneumonia, called EMT was found unresponsive at home. Likely anoxic encephalopathy, also ARDS, shock liver, Death due to septicemia of unknown source. On (b) (6) (Day 349), the subject experienced a severe SAE of septicemia. According to the CIOMS report, the subject was ill with nausea and vomiting for approximately 7 days prior to hospital admission. On (b) (6) (Day 349), the subject had a seizure and aspirated, which precipitated a chemical pneumonitis. The subject called emergency medical services on the same day, was found unresponsive by the emergency personnel, and was transported to the emergency department. This led to the subject being admitted to the hospital for respiratory failure and septicemia. Abnormal laboratory results on admission included increased liver function and arterial blood gas tests, as shown in the table below. The subject also had acute respiratory distress syndrome, cerebral edema, shock liver, and metabolic acidosis. The subject was intubated. On (b) (6) (Day 350), a CT scan of the brain revealed findings that were highly suggestive of generalized cerebral edema due to global anoxic insult. Day 349	complications of seizure related aspiration after 1 year on treatment.
(b) (6)	YKP3089C017 OLE	SUDEP	129	300	27 yo male, right anterior temporal lobectomy with hippocampectomy. 400mg YKP in DB on day 128 , Found dead by roommate on day 129. The subject was found deceased by a roommate on (b) (6) (Day 129). The investigator believed the event to be a case of sudden unexpected death in epilepsy with sinus bradycardia and hot water exposure contributing, a cardiovascular event with hypotension, or other causes. The	SUDEP, uncertain relationship

Subject ID	Study Number	PT term(s)	Dose	Study day	History	Comment
					autopsy found no major trauma or other physical findings contributory to death. Additional clinical information revealed that the subject was in considerable stress around the time of death, which may have contributed to a possible autonomic nervous system mediated event.	
(b) (6)	YKP3089C017 OLE	completed suicide	100	1373	On (b) (6) (day 1499), the subject experienced the fatal event of suicide (previously reported as death-suicide). The subject had a quarrel on (b) (6) with his wife, following which he left the house. On (b) (6), the subject was found to have hanged himself. The subjects cause of death was confirmed by the death certificate to be sudden asphyxiation through hanging. An autopsy was performed on (b) (6) but the report is not available	completed suicide after 3.8 years of treatment has poor temporal relationship to support causality.
(b) (6)	YKP3089C017 OLE	pneumonia and sepsis	241	300	57 yo m, diagnosis was reported as lung and heart failure caused by sepsis with endotoxic shock. Sepsis was confirmed to be secondary to pneumonia (d 241). Microbiological investigations from the lung revealed positive Klebsiella spp. No clear data regarding the course of event prior to hospitalization were available. On admission to the hospital, there was no evidence of head trauma. There was no confirmation of aspiration; however, the subject's breathing was worsening. The subject required increased ventilatory support, progressing from assisted mechanical ventilation to total mechanical ventilation due to worsening ventilatory compliance. The primary diagnosis for the subject was bilateral pneumonia with ventilation failure. No Evidence of aspiration. Death day 253	sepsis and pneumonia of uncertain etiology. No report of preceding seizure or aspiration
(b) (6)	YKP3089C017 OLE	cardiogenic shock	840	200	39 yo male, pt on 100mg/day for 762 days at time of "cardiogenic shock" on day 840. On (b) (6) an autopsy showed no signs that could relate to violent trauma. The autopsy results were reasonably consistent with a natural death, with the immediate cause of the subject's death noted as cardiogenic shock, due to underlying istopic cardiopathy and severe coronary arteriosclerosis.	an unexplained fatal cardiogenic shock without preceding signs or symptoms. There is no temporal relationship, the event occurred after 2.3 years of treatment. A TEAE of dyslipidemia was entered on study day 384.
(b) (6)	YKP3089C017 OLE	road traffic accident	317	400	27 yo male struck by an automobile as a pedestrian Day 317	not physiologically related to Cenobamate treatment
(b) (6)	YKP3089C020	eosinophilic myocarditis			38 yo F in TQT Study, DRESS day 32 of cenobamate treatment. On day 32 of treatment and 10 days of cenobamate treatment at 200mg the patient developed a rash on face and neck. On day 39 (treatment discontinued on day 32) the rash continued	DRESS due to study drug

Subject ID	Study Number	PT term(s)	Dose	Study day	History	Comment
					to worsen, and the patient presented to study site with rash over the entire upper body but no mucosal lesions. The patient also complained of nausea, right mid back pain and a sensation of difficulty breathing and need to cough. Pulse-Ox was 96% on room air. ALT and AST were found to be 238 and 187 respectively. Skin biopsy was consistent with DRESS syndrome. The patient condition continued to worsen including elevation of ALT and AST of 616 and 414. Prednisone treatment was discontinued on day 64 but the patient was subsequently found dead at home on day 84, 51 days after cessation of study drug.	
(b) (6)	YKP3089C021	laryngospasm	100	142	21 yo F, Angelman syndrome, on lamotrigine, clobazam, clorazepate. UTI day 46 hospitalized, respiratory failure/pneumonia, extended hospitalization and rehab. Respiratory failure DNR (court agreement to extubate) Expired day 142 Pt remained on study drug. Relevant medical and surgical history included: VNS implant on (b) (6) attempted tracheostomy with collapsed lung in (b) (6) Angelman syndrome, ongoing since (b) (6) hip dysplasia, ongoing since (b) (6) scoliosis, ongoing since (b) (6) pneumonia, ongoing since (b) (6) pancreatitis, ongoing since (b) (6) pneumothorax on (b) (6) dysphagia, ongoing since (b) (6) and allergies, ongoing since (b) (6). On (b) (6) (study day 46), the subject experienced the mild SAE of urinary tract infection and the moderate SAE of dehydration. The subject was taken to the ED on (b) (6) and admitted to the hospital. On (b) (6) the subject experienced the moderate SAEs of acute respiratory failure with hypoxemia and aspiration pneumonia. The subject was intubated during this hospitalization and was treated with piperacillin-tazobactam. The subject failed multiple trials of extubation due to laryngospasm and underwent tracheostomy on (b) (6) She was transferred to a rehabilitation facility	severe underlying medical compromise, likely urosepsis and aspiration pneumonia with prolonged endotracheal intubation
(b) (6)	YKP3089C021	SUDEP	282	250	46 yo male, found dead in bed after 282 days of treatment, no premorbid symptoms. Hx head injury. AEDs : VPA, CBZ, LTG //The family informed the investigational site staff that the subject died during his sleep on (b) (6). On (b) (6) the subject's mother reported to site staff that the subject did not report any complaints on (b) (6). On the morning of (b) (6) the subject awoke, used the bathroom, and then	SUDEP, uncertain relationship

Subject ID	Study Number	PT term(s)	Dose	Study day	History	Comment
					returned to his bedroom. The subject's mother found him deceased in his bed at 0730.	
(b) (6)	YKP3089C021	traumatic intracranial haemorrhage	75	150	60 yo male, fell during witnessed seizure and struck head. large right temporal intraparenchymal hemorrhage with subdural and subarachnoid blood, 11mm midline shift and developing hydrocephalus. Life support discontinued study day 75. Prior seizure with fall and intracranial hemorrhage on day 23 (effective?)	head injury associated with seizure x 2 raises possibility of medication ineffective for this patient.
(b) (6)	YKP3089C021	hypovolemic shock	117	200	63 yo female the subject experienced severe and fatal SAE of hypovolemic shock. The event occurred as the subject was crossing the street and was struck by an automobile, resulting in immediate death, study day 117 Receiving 200mg for six weeks	unrelated traumatic death

Figure 16 Death in Development Program, Study Day vs Dose by Cause of Death



Death, Reviewer Summary:

There were 16 deaths during the development program, 15 were on treatment and 1 during baseline (not on study drug treatment). This count includes the 120-day safety update, representing 0.8% of patients exposed to Cenobamate. Eleven of the events occurred within 349 days of Cenobamate treatment initiation while the remaining 4 events occurred after 1.9 years of treatment. No deaths occurred in the treatment or placebo arms of the double-blind study intervals (12 weeks in study C013 and 18 weeks in study C017). There were 2 suicides, one that occurred after 132 days of Cenobamate treatment, 46 days after entering the open label phase, the second occurred after 3.7 years of Cenobamate treatment. There were two traumatic deaths, both instances of pedestrian patient struck by an automobile. In one case, the report states the patient was killed on the "highway" with no other information provided. If this event occurred on a limited access type of transit, it may represent a suicide due to the unusual nature of a pedestrian entering such an environment. However, this is speculative. There were 3 SUDEP events, this frequency does not exceed the frequency reported overall in patients with refractory epilepsy. There were 3 cardiogenic events, none before 1.9 years of treatment, one in a 39-year-old male after 2.3 years of treatment with little explanation but no compelling temporal relationship to Cenobamate treatment. There were 3 deaths related to infection, two subsequent to pneumonia. From among the 2 due to pneumonia one was due to an aspiration during a seizure. The 3rd infection related death followed a urinary tract infection in a medically fragile patient. There was one death due to a seizure with associated head injury and a death due to DRESS at day 84 in the thorough QT study.

Reviewer Comment: there is temporal dispersion of death events with variation in the category of underlying medical characteristics of the events. There is absence of clear causal relationship in all but the subject who developed DRESS. Analysis of the deaths in development reveal a death risk related to DRESS.

8.4.2. Serious Adverse Events

C013 & C017 Double Blind Pool

SAEs by SOC with Greater Than a Single Event

Serious adverse events were examined in the pivotal study double blind pool of studies C013 and C017. This pool contains a total of 659 patients randomized into studies C013 and C017. One placebo patient was not treated. In the pooled group there were 108, 223, 111, and 216 patients in the 100mg, 200mg, 400mg and Placebo treatment arms respectively, see [Table 22](#), [Figure 17](#) and [Figure 18](#).

Nervous System Disorders

The highest frequency of SAEs was occurred in the “Nervous System Disorders” SOC with a total of 18 SAE entries, where the most frequent preferred term was “seizure”. Under the preferred term seizure there were 2 events in the 100mg treatment arm, 1 in the 200mg treatment arm and 1 in the 400mg treatment arm. The highest frequency in the lowest dose arm may be related to the low end of the dose response curve. One SAE of status epilepticus occurred in the 200mg treatment arm. The remaining SAE events in Cenobamate treatment arms occurred under the preferred terms Ataxia, Dizziness, lethargy, hemiparesis, nystagmus, and somnolence. There was a trend of dose response for non-seizure related preferred terms where SAEs occurred in 1.9% of patients in the placebo arm, 3.7% of patients in the 100mg treatment arm, 0.9% of patients in the 200mg treatment arm and 7.2% of patients in the 400mg treatment arm.

Reviewer Comment: Serious adverse events in the “Nervous System Disorders” SOC were the most frequent. Epilepsy related events of “Seizure”, “Status Epilepticus”, and “Convulsion” were half of events where the other half were primarily related to CNS dysfunction. The only SAEs in the placebo arm were epilepsy related where 4 events occurred, including one convulsion and 3 status epilepticus. The distribution of the central nervous system adverse effects was greatest in the 400mg arm. This is an expected distribution.

Injury, Poisoning and Procedural Complications

There were 10 SAEs (9 unique patients) in the category of “INJURY, POISONING AND PROCEDURAL COMPLICATIONS”, 2 in the placebo and 8 with Cenobamate treatment. Two of these events were seizures accompanied by a fall, both in the placebo arm.

From among the events in the cenobamate treatment arms there were 8 events that occurred in 7 unique patients. There were three events of fall that, one of these events coded under the preferred term of “facial bones fracture” where the patient fell and struck his face on the

bumper of an automobile. The facial bone fracture occurred on study day 44 at a Cenobamate dose of 400mg while another of the “fall” events occurred on study day 42 on a Cenobamate dose of 400mg. The third and final fall entry in the “INJURY, POISONING AND PROCEDURAL COMPLICATIONS” SOC appears to be secondary to an event of agitation when the patient threw herself on the floor. There is no background on the SAE of “Femur fracture”, the sponsor reports due diligence in multiple attempts to obtain additional background information. The entry in this SOC of “thermal burn”, also included in the “PSYCHIATRIC DISORDERS” SOC, occurred during a suicide attempt. Two events that included “limb injury” and “hand fracture” are identified from a single patient where the narrative indicates “performing manual labor”. The final event in this category was a “laceration” that occurred when a patient slipped while using scissors.

Reviewer Assessment: The events of fall and injury are likely due to the central nervous system effects of cenobamate. The event of “thermal burn” was related to a suicide attempt.

Psychiatric Disorders

There were 3 events from three unique patients treated with Cenobamate in the SOC “psychiatric disorders”. Three were 2 events of suicidal ideation and one event of suicide attempt all in the 100mg treatment arm.

Reviewer Comment: Suicide and suicidality risk are a class effect of Antiepilepsy drugs. In the DB dataset there were three suicidality events (no completed suicide) in cenobamate treatment and none in placebo. This supports continued class effect signal for this AED.

Investigations

Among patients in the cenobamate treatment arm there were 3 events from a single unique patient. These events were aspartate aminotransferase increased, alanine aminotransferase increased, and immunoglobulins decreased. Treatment was discontinued. When rechecked 5 days later rapid improvement in the ALT and AST values were noted. When normalized to the ULN ALT values declined from 7.6 to 4.2 while AST values declined from 3.8 to 1.4. During this interval there was a mild increase in alkaline phosphatase level to 1.4 x ULN. The decline in immunoglobulin values was observed in samples obtained 13 days after cenobamate discontinuation where IgA and IgM values were found to be 0.6 and 0.7 x LLN respectively. These measurements were repeated at 28 days post cenobamate treatment with little change in value. No baseline IgA and IgM values are available.

Infections and Infestations

There were 3 events from 3 patients. Two of three events occurred in the placebo treatment arm. The preferred terms of these events were “infectious colitis” and “abscess jaw”. In the 200mg cenobamate arm there was an entry with the preferred term “urinary tract infection”.

This event started on study day 35 and resolved on study day 37 and is reported as resolved and of moderate severity by the investigator

Reviewer comment: During the double-blind interval there were SAEs in the SOC of infection events in 0.9% of the placebo group and 0.4% of the cenobamate 200mg treatment arm. In this interval there is no signal for infection vulnerability associated with cenobamate treatment.

SOCs with a Single SAE

The remaining 6 SAE entries occurred in six unique patients in the categories shown in [Figure 18](#). From among these there were two due to drug hypersensitivity. One event, drug hypersensitivity was entered in the “Immune system disorders” SOC while the second event DRESS was entered in “skin and subcutaneous tissue disorders” SOC. The patient (YKP3089C013- (b) (6)) with an entry of “drug hypersensitivity” developed flushed erythema of palms and soles with mild itching of ears after the first dose of cenobamate and was treated in the emergency department with oral methylprednisolone and antihistamines. Five days later the patient was examined and had continuation of these findings. The reaction is reported resolved 21 days after the single dose of cenobamate. The second patient (YKP3089C017- (b) (6)) had a starting dose of 100mg cenobamate during week 1 of treatment, scheduled to advance to 200mg during week 2. On study day 24 where according to schedule the patient was taking 200mg cenobamate for 16 days, the patient developed diffuse macular erythematous and pruritic rash covering the majority of body surface area including the face, trunk, back, arms, and legs; headache; arthralgia; myalgia; and memory problems. Bilateral pleural effusions were also present. Cenobamate was discontinued on study day 24. The patient was treated with antihistamines and methylprednisolone 60mg IV every 8 hours. The patient was discharged after a 7-day inpatient admission. Subsequent emergency room evaluations are documented on study day 35 and 39 for rash. The patient was then lost to follow up. Outcome of the DRESS event remains unknown, see [section 8.5.1](#).

Reviewer Comment: The occurrence of a notable and persistent erythema and pruritis after a single dose of cenobamate is consistent with a high potential to generate a hypersensitivity response. The second case in this discussion is more severe, with multisystem involvement and serositis. In this second case, the adverse event occurred in the scheme of rapid cenobamate escalation (reduced in later protocol iterations). Again, this emergence of DRESS is consistent with the high hypersensitivity potential of cenobamate. These two cases are causally related to cenobamate therapy.

Among the remaining 4 events, there was one event each in the SOC of RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS, GASTROINTESTINAL DISORDERS, MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS and EAR AND LABYRINTH DISORDERS. The event in the “gastrointestinal disorders” SOC was an adverse event preferred term “gastroesophageal reflux”. occurred in the placebo arm. The remaining three events were “pulmonary embolism”,

“musculoskeletal chest pain” and “vertigo”. Because of the possible relationship of a pro-thrombotic state to a pro-inflammatory state, the event of “pulmonary embolism” will be explored further.

YKP3089C017-(b) (6) (PT pulmonary embolism): a 41-year-old Caucasian male who was admitted to the hospital on study day 24 for suspected stroke. The patient had worsening of a pre-existing right hemiparesis and a new infarct was suspected. During the evaluation asymptomatic pulmonary emboli were found incidentally, in one of the innominate arteries in the chest. The outcome is identified as recovered, the patient was begun on warfarin. Cenobamate was discontinued on study day 24.

Reviewer Comment: The patient apparently had sedative adverse effects during the introduction to cenobamate. The narrative indicates that activity was reduced. The worsening of right hemiparesis was likely due to functional worsening the pre-existing left fronto-temporal encephalomalacia due to cenobamate associated CNS depression. Causal relationship is association only.

Table 22 Pivotal Study DB Pool (C013 & C017), Distribution of SAE's by Treatment Arm, SOC and PT, Shown by Count and Percent of Dose Group

SOC	PT	100mg		200mg		400mg		PBO	
		# pts	%	# pts	%	# pts	%	# pts	%
EAR AND LABYRINTH DISORDERS	VERTIGO					1	0.90		
GASTROINTESTINAL DISORDERS	GASTROESOPHAGEAL REFLUX DISEASE							1	0.50
IMMUNE SYSTEM DISORDERS	DRUG HYPERSENSITIVITY			1	0.40				
INFECTIONS AND INFESTATIONS	ABSCESS JAW							1	0.50
	INFECTIOUS COLITIS							1	0.50
	URINARY TRACT INFECTION			1	0.4				
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	CONCUSSION							1	0.50
	FACIAL BONES FRACTURE					1	0.90		
	FALL			1	0.40	1	0.90		
	FEMUR FRACTURE			1	0.40				
	HAND FRACTURE	1	0.90						
	JAW FRACTURE							1	0.50
	LACERATION	1	0.90						
	LIMB INJURY	1	0.90						
	THERMAL BURN	1	0.90						
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED					1	0.90		
	ARTERIOGRAM CORONARY NORMAL							1	0.50
	ASPARTATE AMINOTRANSFERASE INCREASED					1	0.90		
	IMMUNOGLOBULINS DECREASED					1	0.90		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	MUSCULOSKELETAL CHEST PAIN	1	0.90						
NERVOUS SYSTEM DISORDERS	ATAXIA					2	1.80		
	CONVULSION							1	0.50
	DIZZINESS					2	1.80		
	HEMIPARESIS	1	0.90						
	LETHARGY	1	0.90						
	NYSTAGMUS					2	1.80		
	SEIZURE	2	1.90	1	0.40	1	0.90		
	SOMNOLENCE					1	0.90		
	STATUS EPILEPTICUS			1	0.40			3	1.40
PSYCHIATRIC DISORDERS	SUICIDAL IDEATION	2	1.90						
	SUICIDE ATTEMPT	1	0.90						

SOC	PT	100mg		200mg		400mg		PBO	
		# pts	%	# pts	%	# pts	%	# pts	%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	PULMONARY EMBOLISM	1	0.90						
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS			1	0.40				
Total SAE Events		13		7		14		10	
Total Unique Patients / Dose Group		10		7		8		10	

Figure 17 Pivotal Study DB Pool (C013 & C017), Distribution of SAE's by % Treatment Arm (Unique Patients)

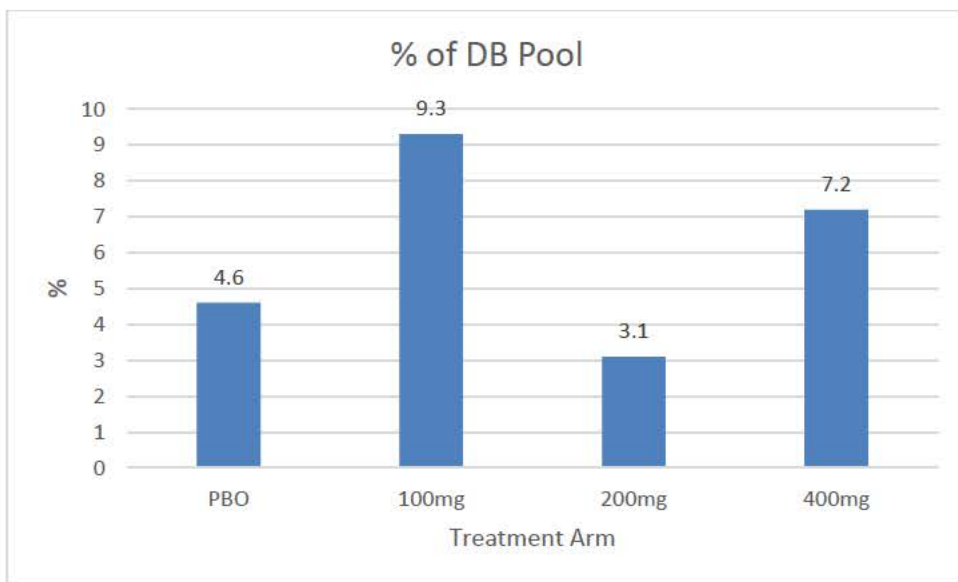
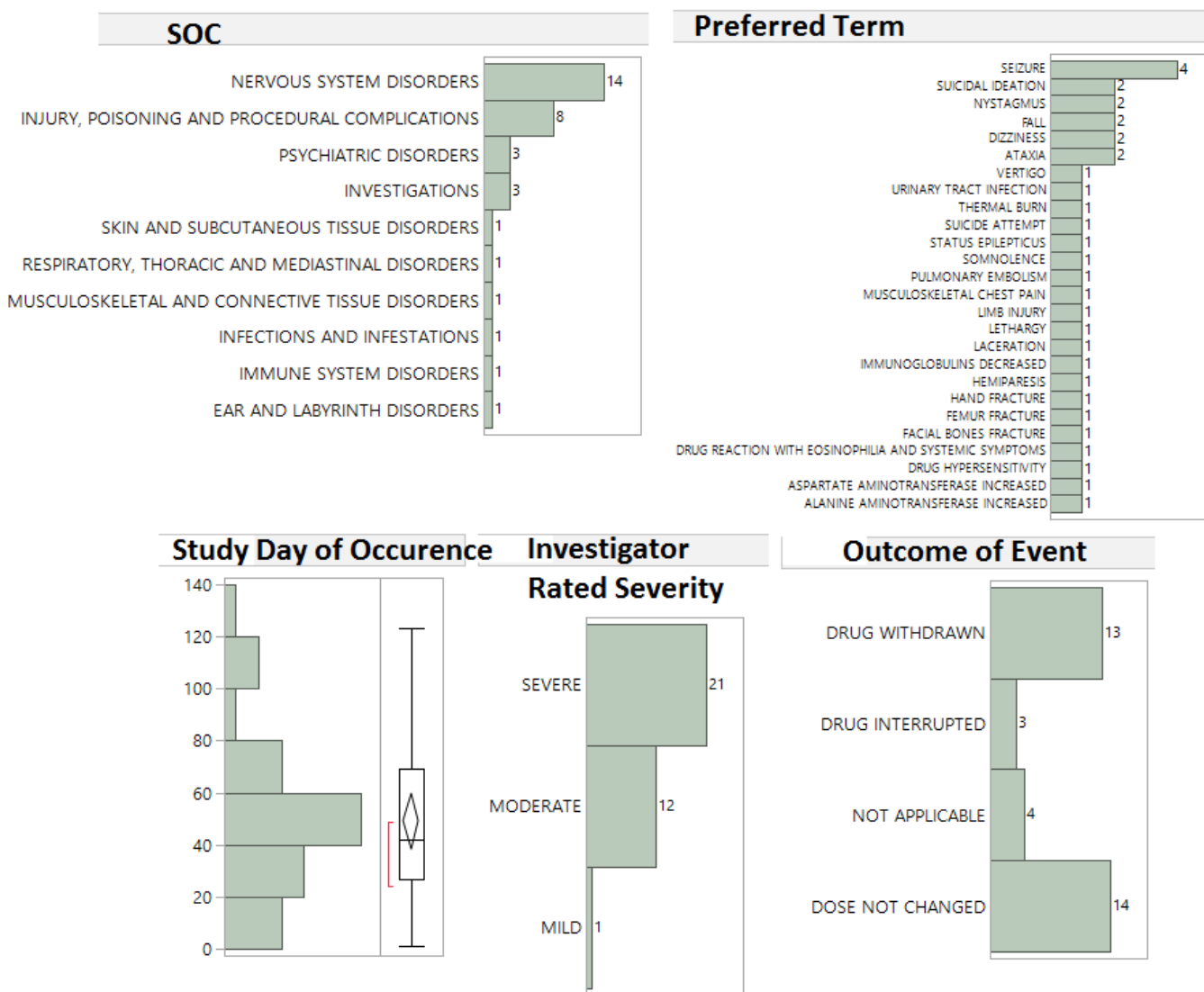


Figure 18 DB Pool, C013 & C017, Characteristics of SAE Distribution in Cenobamate Treated Patients.



Reviewer Comment: Analysis of serious adverse events in the double-blind period reveals a higher frequency overall in the cenobamate treatment arms but without a clear dose response relationship. The most frequent adverse events in the placebo arm are events related to epilepsy, where seizure terms almost equally divided between placebo and treatment arms and there is a minimum in the 400mg arm. “Nervous System Disorder” events that predominate in the cenobamate treatment arm are related to central nervous system dysfunction, suicidality, and drug hypersensitivity. The safety events to consider for labeling are central nervous system adverse events, drug hypersensitivity and suicidality. These are present in proposed labeling. The event of ALT elevation entered as an SAE during the double-blind treatment period reached a maximum of 7.6 x ULN while on 400mg cenobamate. The ALT value improved to 2 x ULN 12 days after study drug discontinuation. A single event of “pulmonary embolism” occurred in the

100mg cenobamate treatment arm associated with a cerebral infarction. This event may have been related to change in physical activity. An overall pro-thrombotic state could unify the cerebral infarction and pulmonary embolism. This single event without clear causality does not provide support for a mechanistic relation to cenobamate.

C013-C017 OLE

A C013-C017 Study pool is derived from the 120-day ISS. Studies C013 and C017 are selected. From this subset all entries that have a “Y” entry for C013 and C017 open label safety flag are selected (SF13OLFL & SF17OLFL). Treatment day is calculated by subtracting the cenobamate treatment start date (YKPSDT) from the adverse event start date (AESDT). Finally, all treatment start dates with a value of ≥ 1 are selected to yield an adverse event dataset with 4479 entries (rows) from 464 patients. The “Y” serious adverse event flag is selected from this set to yield 173 SAEs from 114 patients.

Fatal events and cenobamate discontinuations are excluded from this dataset and are covered in sections 8.4.1 and 8.4.3 respectively.

There were 24 preferred terms with a frequency in >1 patient, see [Table 23 Table 23 SAE, Studies C013 & C017 Pooled Open Label Extension, Preferred Terms with Frequency >1 Patient \(0.4%\)](#).

Table 23 SAE, Studies C013 & C017 Pooled Open Label Extension, Preferred Terms with Frequency >1 Patient (0.4%)

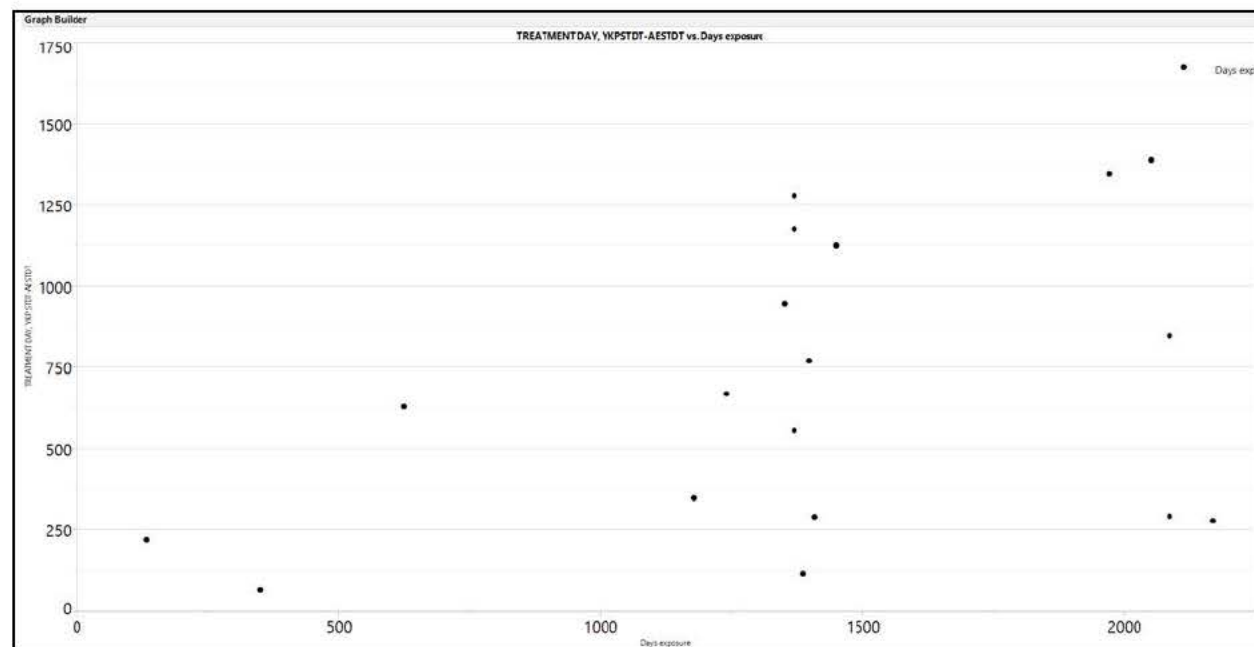
PT	Patient Count	% Patients
Seizure	13	2.6
Pneumonia	4	0.8
Sepsis	4	0.8
Vertigo	4	0.8
Dizziness	3	0.6
Seizure cluster	3	0.6
Accidental overdose	2	0.4
Cardiac arrest	2	0.4
Cholecystitis acute	2	0.4
Cholelithiasis	2	0.4
Completed suicide	2	0.4
Concussion	2	0.4
Epilepsy	2	0.4
Generalised tonic-clonic seizure	2	0.4
Hand fracture	2	0.4
Humerus fracture	2	0.4
Myocardial infarction	2	0.4
Osteoarthritis	2	0.4
Pulmonary embolism	2	0.4
Pyelonephritis	2	0.4

PT	Patient Count	% Patients
Road traffic accident	2	0.4
Sudden unexplained death in epilepsy	2	0.4
Urinary tract infection	2	0.4
Vomiting	2	0.4

Discussion of key selected events m (occurrence may be any >0):

Epilepsy Events, SAE entries: There were 13 patients with an entry for “seizure”, two patients with an entry for “epilepsy”, three patients with an entry for “seizure cluster” and two patients with an entry for “generalized tonic clonic seizure”. This are a total of 20 patients with epilepsy events. *Causal Assessment: These events are distributed across a long timeline of cenobamate exposure with no clear coupling between the seizure event and duration of exposure, Figure 19. This property reduces a causal pro-convulsant relationship between cenobamate and seizure occurrence. This uncoupled pattern also reduces the likely of loss of effectiveness as the underlying cause of seizures.*

Figure 19 Studies C013-C017 Open-Label Extension, Plot of Time of Epilepsy Event vs Time of Total Exposure Duration by Individual Patients.



Infection Entries: The identification of 4 patients with a preferred term entry “pneumonia” where 2 of these patients have and entry for “sepsis”. Two additional patients also have an

entry for “sepsis”. The laboratory dataset for these 6 patients is examined for abnormalities in hematologic parameters as well as the patient with the single entry for “appendicitis” and the patient with an entry for “Appendicitis perforated” (0.4% each). This assessment reveals that patients YKP3089C017-^{(b) (6)} and YKP3089C013-^{(b) (6)}, preferred terms of “appendicitis” and “pneumonia & Sepsis” respectively, had a mild reduction from baseline in values for neutrophils. Patient YKP3089C013-^{(b) (6)}, with a preferred term entry for “sepsis” and “urosepsis” had an elevation of leukocytes, lymphocytes and neutrophils noted between 30 and 66 months. Two patients with the preferred term “urinary tract infection” are also included in the analysis. One of these patients (YKP3089C013-^{(b) (6)}) had two (episodic) entries for leukocytes out of reference range (OORR) low and the second patient (YKP3089C017-^{(b) (6)}) had a sporadic entry of lymphocytes OORR low. *Causal assessment: Overall, these infections do not appear related to systematic or sustained myelosuppression.*

Myocardial Infarction: There were two patients with a preferred term entry for “myocardial infarction”. Patient “YKP3089C017-^{(b) (6)}” had a fatal event that is also presented in section 8.4.1. Patient “YKP3089C017-^{(b) (6)}” was a 60 yo female with a prior history of cardiovascular disease who had a fatal myocardial infarction on study day 1142. Patient “YKP3089C017-^{(b) (6)}”, a 47 yo Caucasian male with a 7-year history of hypertension who also has bronchial asthma, developed intermitted shortness of breath and numbness in hands. Upon hospitalization on study day 1122 there was a diagnosis of myocardial infarction, semi-posterior. The patient had stent placed in the obtuse marginal branch. The exposure dataset reveals that cenobamate was continued until treatment day 1366. A third patient in the OLE dataset (YKP3089C013-^{(b) (6)}) had a preferred term entry of “cardiac arrest”. This 58 yo Caucasian male developed right side chest pain radiating to his back on 200mg cenobamate treatment day 695. First responders witness a cardiac arrest upon arrival, but the patient did not survive. This patient does not have cardiovascular risk in the medical history, however the sudden cardiac arrest in the context of thoracic pain are likely due to a cardiovascular cause. *Causal Assessment: These serious cardiovascular events occurred on average 2.7 years after beginning of cenobamate treatment. In one patient there was prior cardiovascular disease. In the second, younger patient, there is a history of hypertension. The third patient, entered as “cardiac arrest”, was a 58 yo Caucasian male with no documented cardiovascular risk history. The long latency to the myocardial infarction in all reports. In 2 of the 3 cases there is a plausible cardiovascular risk history. The long latency to the cardiac event in addition to 2 patient histories confounded by cardiovascular risk in the context of an adverse event with a high background rate “myocardial infarction”⁹, do not support conclusion of a causal relationship to cenobamate.*

Cardiac Arrest: There were two patients with an entry for “cardiac arrest”. The first, fatal case, patient YKP3089C013-^{(b) (6)}, is discussed in sec 8.4.1 and is also entered above in the discussion of reports of the preferred term “myocardial infarction”. In the second case, patient

⁹ Mozaffarian D et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. 2015 Jan 27;131(4):e29-322. doi: 10.1161/CIR.000000000000152. Epub 2014 Dec 17.

YKP3089C017- (b) (6), a 33 yo Caucasian male experienced a severe SAE of ictal asystole on study day 1141 and was hospitalized. During routine electroencephalogram (EEG) monitoring as part of an epileptic pre-surgical study, an ictal asystole was recorded during a complex partial seizure. The asystole lasted for 60 seconds. The subject fully recovered after the seizure and it was noted that the seizure characteristics were similar to the subject's usual recorded seizures with the exception of an ictal asystole seizure characteristics were similar to the subject's usual recorded seizures with the exception of an ictal asystole which had never been recorded. The patient subsequently had a pacemaker implantation. *Causal assessment: The linkage to seizure support an ictal neurocardiac or autonomic basis for the event. The long latency from start of cenobamate also reduce support for a causal relationship to cenobamate treatment.*

PT Pulmonary Embolism:

There are 2 patients with the adverse event term "pulmonary embolism" identified in the OLE dataset. One report, patient YKP3089C017- (b) (6), event on treatment day 183. This same patient was found to have an underlying pro-coagulant condition including lupus anticoagulant and heterogeneous status for a G20210A (Factor II) mutation which increases clotting risk. The second patient YKP3089C013- (b) (6), a 48 yo African-American male experienced the moderate SAE of pulmonary embolism on cenobamate treatment day 1897 at a dose of 350mg. The subject presented to the Emergency Department (ED) after 3 days of pleuritic chest pain. The pain was described as constant with fluctuating intensity, starting after an insect bite. An electrocardiogram was normal, chest x-ray showed clear lungs, no pneumothorax or pleural effusion; however, the thorax was positive for acute left lower lobe segmental pulmonary embolism. The subject was stable with unremarkable vital signs, was not hypoxic and was considered stable for outpatient treatment with anticoagulants for a period of 4 to 6 months. Cenobamate treatment was continued. *Assessment: The 1st case of pulmonary embolism was associated with underlying pro-coagulant state. In the second case there was a long, 5.2 year, time to onset from start of cenobamate treatment although there was no reported medical history captured, that provides an explanation for the event. Causal Assessment: One case occurred without underlying, pre-existing cause. This report has a very long latency to the adverse event. This long latency allows for a long background of non-captured, confounding etiologies, that could be drivers to the event. A causal relationship to cenobamate treatment is not supported.*

PT "road traffic accident" YKP3089C017- (b) (6):

Day 295), the subject experienced a severe SAE of car accident. According to the CIOMS report, the subject was hospitalized after a single vehicle crash where the subject's car collided with a tree on the same day. The accident was suspected to be secondary to having a seizure.

PT Cerebrovascular accident YKP3089C017- (b) (6):

(Day 50), a 70 yo African American male experienced a severe SAE of stroke. According to the CIOMS report, the subject had a history of 2 prior strokes, which presented with a history of 1.5

weeks of left upper extremity weakness. The subject experienced the current stroke event manifesting as left-sided weakness as well as headache and clumsiness for 3 days and was seen at the principal investigator's clinic on [REDACTED] (b) (6) (Day 52). An MRI scan was obtained on an unknown date, and magnetic resonance angiography showed a right internal carotid occlusion and string of pearls sign at the borderline region of diffusion on the right side between the middle cerebral artery and anterior cerebral artery, associated with flair hyperintensities. The mechanism for the infarct appeared to be acute and chronic atherothrombotic/embolic disease resulting in right frontal lobe stroke and watershed infarcts. The patient was treated with cilostazol and atorvastatin. Cenobamate treatment was continued. *Causal Assessment: This event occurs on a background of pre-existing cerebrovascular risk. There is a temporal relationship to start of cenobamate treatment which offers some support for causality.*

PT Vision blurred YKP3089C017-[REDACTED] (b) (6):

51-year-old white female with hypoplasia of the left PCA. On study day 16 the patient experienced a left PCA territory infarction, 'cerebral infarction'. On study day 29 the patient experienced "vertigo" and "dysarthria" and was hospitalized for reassessment of cerebrovascular status. No acute cerebral ischemia was identified There was new V1 to v3 T wave inversion. A patent foramen ovale was also identified. The patient was taking cenobamate 300mg at the time and dose was not changed. On study day 64 the patient experienced "dysarthria" and in the emergency room also reported a headache. An episode of "blurred vision" was reported the following day (study day 65). The left occipital infarct previously identified (Left PCA territory) was unchanged. *Causal Assessment: The most threatening event of occipital infarct occurred on study day 16. Causal relationship to cenobamate is confounded by a prior history of prior PCA stroke and patent foramen ovale. Patent foramen ovale has an independent thromboembolic risk. It is uncertain if all the following events across day 29 to 65 were related to recurrent ischemia or these were central nervous system dysfunction related to study drug.*

Table 24 C013-C017 OLE Pool, Patient YKP3089C017-[REDACTED] (b) (6), Sequence of SAEs

Preferred term	TREATMENT DAY, YKPSTDT-AESTDT
Cerebral infarction	16
Dysarthria	29
Vertigo	29
Dysarthria	64
Vision blurred	65

PT "Balance disorder", YKP3089C017-[REDACTED] (b) (6):

a 34-year-old white female (Day 1192), the subject experienced a moderate SAE of abnormal balance and was hospitalized. The subject was admitted to the neurology department due to diplopia and difficulty walking after a seizure. Neurological examination on admission revealed diplopia in all directions with unsteady gait and a Romberg's test was performed. Antiepileptic treatment was continued, and no further seizures were observed while hospitalized. the

subject also experienced nonserious AEs of myoclonus and diplopia. (Day 1197), the subject continued experiencing abnormal balance, which was moderate in severity and resulted in dose reduction. (Day 1203), a cerebral MRI scan was performed, showing no perceptible structural pathologies. The dose of YKP3089 was decreased to 250 mg QD on (Day 1218), decreased to 200 mg QD on (Day 1303), and decreased to 150 mg QD on (Day 1310). (Day 1311), the moderate event of abnormal balance was considered recovered or resolved with sequelae.

Causal Assessment: The adverse events of balance disorder in this case were coupled to cenobamate dose. Causal relationship is very likely. This observation appears to show that long exposure to cenobamate does not ensure full adaptation to the central nervous system adverse effect of cenobamate.

PT “vertigo”, YKP3089C017- (b) (6):

28-year-old white female (Day 377), the subject experienced a mild AE of vertigo. On (b) (6) (Day 537), the AE worsened to a severe SAE of vertigo and the subject was hospitalized. According to the CIOMS report, the subject was admitted due to dizziness, imbalance, and nausea that had been persisting and worsening over the last 3 days. A neurological examination on admission found horizontal nystagmus, an unsteady Romberg’s test, and a tendency for plantar reflex on the left. (Day 537), an ECG showed regular sinus rhythm 60 bpm and flattened T waves in most leads; a head CT scan revealed asymmetric vestibulocochlear nerve canals; and a head MRI scan revealed a minor angiogenic lesion in the left frontal lobe. Administration of investigational product was maintained. During hospitalization, dizziness and nystagmus were observed to have worsened which correlated with the time of investigational product administration. (Day 540), the dose of study drug was decreased to 150 mg QD due to the event. On (Day 541), the subject was discharged from the hospital and the outcome of the event of vertigo was recovered or resolved with sequelae of moderate nonserious vertigo.

Causal Assessment: This report reveals a coupling between the central nervous system adverse events of vertigo, dizziness, and imbalance and the dose of cenobamate event after a long period of exposure. Causal relationship is confirmed by the dechallenge response to cenobamate dose reduction.

PT “Appendicitis “ YKP3089C017- (b) (6):

37-year-old white male was (Day 1267), the subject experienced a severe SAE of appendicitis and was hospitalized. According to the CIOMS report, the subject was admitted to the hospital due to abdominal pain, which was then diagnosed as appendicitis. The subject underwent a successful operation. Two prior admissions for seizure breakthrough beginning day 1073.

PT “Appendicitis” YKP3089C017- (b) (6):

A 39-year-old male has an SAE entry for the preferred term “appendicitis perforated” on study day 592 at a cenobamate dose of 200mg.

Causal Assessment: These two events are not temporally related the start of cenobamate treatment, however, the overall study C013, C017 and C021 safety database reveal a higher

frequency of appendicitis than typical background rate, see Appendicitis, section 8.4.3 for expanded discussion.

PT “enterocolitis”, YKP3089C017- (b) (6):

31-year-old Asian male (Day 686), the subject experienced a severe SAE of enterocolitis and was hospitalized on (Day 687). According to the CIOMS report, the subject had reported feeling unwell with abdominal pain that gradually worsened. An ultrasound and an abdominal colonoscopy were performed, and the subject was diagnosed with simple abdominal pain associated with enterocolitis. The subject was treated with unspecified medications for pain and intravenous fluids, and the symptoms improved without any surgical intervention. The investigator considered the severe SAE of enterocolitis remotely related to the study drug. No action was taken with the study drug due to the event. *Causal Assessment: This report was examined to determine if there is a broader occurrence of gastrointestinal dysfunction that may be related to the increased frequency of “appendicitis”. This event alone does not appear causally related to cenobamate but does contribute to the knowledge of the overall landscape of gastrointestinal effects.*

PT “somnolence”, YKP3089C017- (b) (6):

day 39 and vertigo entered day 105 as PT somnolence: 41-year-old white female (Study Day 105), the subject experienced a severe SAE of dizziness. As documented in the CIOMS report, on (b) (6) the subject woke up at night and fell to the ground due to dizziness. No loss of consciousness or head injury was reported; the subject’s right arm was sensitive, but the extremity was functional. *Causal Assessment: This patient has persistent intolerance to the central nervous system effects of cenobamate. There was an SAE of somnolence at study day 39 with additional features of “dysarthria, vertigo, loss of balance, negativism, aggressive speech, and one episode of visual hallucinations” reported on hospital admission. A second SAE of “dizziness” occurred on study day 105. The patient has an underlying history of cerebral palsy which may be a cause of selective vulnerability to CNS dysfunction due to cenobamate.*

PT “psychotic disorder”, YKP3089C017- (b) (6):

30-year-old white male Medical history included herpes encephalitis, partial resection of the temporal lobe, implantation of vagus nerve stimulator, and changing generator of vagus nerve stimulator. (Day 727), the subject experienced a moderate SAE of psychosis not further specified while treated with 400mg cenobamate. The subject reported fears that his neighbor might do harm to him. The subject was subsequently hospitalized due to psychosis not further specified, and brivaracetam was discontinued. Cenobamate was continued at 400mg. *Causal Assessment: The patient’s prior cerebral injury due to herpes encephalitis may cause a vulnerability to psychoactive agents. Causal relationship to cenobamate is uncertain in this case there is no report of discontinuation or dose reduction. The event appears to have spontaneously resolved. There is also a lack of temporal association to support a direct causal link to study drug.*

PT “pericarditis”

YKP3089C017- (b) (6): 67-year-old Hispanic female. On study day 562, the patient experienced a severe SAE of complete left bundle branch block. Prior to the event, the investigator reported that the subject had 1 episode of pre-syncope [Day 190], the subject had felt dizzy during a left foot x-ray with lateral movements of the neck, but without impairment of level of consciousness; the subject was admitted to the emergency room for analysis including a chest x-ray and an EKG), and 1 episode of syncope [Day 326], the subject was hospitalized for dysarthria; a neurologic and physical examination showed mild alteration in recent memory and pain in the right hip; 4 days prior to the event the subject had micturition syncope while urinating and had been hospitalized). (Day 562), the subject reported syncope in the morning and presented to the emergency room. She was walking in the street on her spouse’s arm and suddenly lost consciousness and fell to the ground, partially supported by her husband. an ECG showed complete left bundle branch block with changes secondary to repolarization. An ECG from the past year showed a progressing anterosuperior partial left branch block and subsequent conduction disorder. After evaluation in a clinical meeting, it was considered probable that the syncopal episode could have been related to a complete paroxysmal atrioventricular block, and a tributary pacemaker implantation was recommended (class IIa indicated). (Day 566), the tributary pacemaker was implanted. (Day 568), the subject felt intrascapular pain for 4 hours without other symptoms, and on (b) (6) (Day 569), the subject experienced dizziness and dysarthria. The subject presented to the emergency room with symptoms of dizziness when standing, not associated with other movements, and was readmitted. An ECG showed regular sinus rhythm at 72 beats per minute with ventricular response from the pacemaker; left axis, narrow QRS complex, left anterior hemiblock; and no changes in repolarization. Day 580), the subject experienced a severe SAE of pericarditis. She returned to the hospital with fever up to 39°C and pericarditis was reported. The subject felt mild epigastric pain varying with postural changes and mild somnolence. The cardiologist evaluated the subject in the emergency room and after a thoracic x-ray, CT scan, and echocardiogram, the subject was diagnosed with several pericardial effusions with incipient tamponade signed. A chest x-ray showed cardiomegaly (not previously present) which was attributed to irritative pericarditis probably related to perforation by the articular cable of the pace maker. The investigator considered the severe SAE of complete left bundle branch block possibly related to the study drug, and the severe SAE of pericarditis remotely related to the study drug. Day 605), the subject was discharged from the hospital. A transthoracic echocardiogram at discharge showed removal of pericardial layers and normal biventricular function. The suspected diagnosis was perforation by the atrial lead and secondary irritative pericarditis. A repeat echocardiogram showed no signs of pleural effusion relapse, so the pericardial drain was removed. The subject was diagnosed with cardiac tamponade, probable cardiac perforation from the atrial electrode. *Causal Assessment: This patient had an intraventricular conduction defect identified on baseline ECG. The 1st episode of syncope may have been the earliest manifestation of an emerging conduction disorder. Overall, causal relation to cenobamate is uncertain. It is possible that the baseline intraventricular conduction*

delay is a selective vulnerability for drug related adverse pharmacodynamic effect. The subsequent SAE of "pericarditis" is a procedural related adverse event.

PT "Road Traffic accident" YKP3089C017- (b) (6): (Day 317), the subject experienced a severe SAE of automobile-pedestrian accident which was fatal. The subject was hit by a car on the highway at approximately 20:30 and sustained multiple injuries that proved fatal, and he died at the scene of the accident. 400mg Cenobamate. *Causal assessment: There is insufficient information to judge causal relationship, either due to suicidal intent or other manifestation of central nervous system dysfunction such as somnolence or confusion.*

PT "confusional state"

YKP3089C013- (b) (6): (also psychosis): 40-year-old Caucasian male. Approximately study day 365 while on cenobamate 200mg, the subject developed a group of symptoms and signs including blurry vision, memory loss, confusion and word finding difficulties. He was suspected of having increased seizures at first. The subject was diagnosed with Confusional state. According to the investigator, carbamazepine was tapered off, locasamide was decreased and topiramate was increased, and YPK3089 200 mg/day was continued. An EEG on (b) (6) revealed background slowing and right frontal spike activity. The subject was admitted to the hospital on (b) (6) for EEG monitoring. No significant increased seizure activity was demonstrated. In the hospital, his condition worsened with him developing more irritability, boisterousness, and confusion as well as new perseveration. At times he was aggressive and needed aripiprazole and lorazepam for sedation. On (b) (6) the subject experienced a psychotic episode with delusions, visual and auditory hallucinations and became aggressive and disruptive. He was given a single dose of Lorazepam 2mg IV and then PRN. A psychiatric consult was requested. He was started on Zyprexa 10mg qd. An EEG of (b) (6) showed mild-to-moderate generalized background slowing suggestive of bihemispheric dysfunction, may be seen in toxic or metabolic encephalopathies or primary neurological disorders. An MRI of (b) (6) showed diffuse cerebellar atrophy which could be due to chronic seizure disorder, no evidence of infarct, intracranial hemorrhage and no mass effect or midline shift. On (b) (6) the subject continued to be confused but marginally improved. On (b) (6) the delusions and auditory hallucinations resolved. On (b) (6) the subject was clinically stable. His mental status improved. He continued to have intermittent agitation, but it was less often and less intense. He was close to his baseline and was discharged. Both informed the investigator that the subject is doing very well without any residual effects of the SAE. Study Drug was discontinued on study day 382. *Causal Assessment: No clear underlying vulnerability to psychoactive drugs is identified in the medical history. A causal association is supported by a positive dechallenge response (potentially confounded by antipsychotic drug treatment).*

Study C021

Serious adverse events in study C021 were examined using the 120 day SDTM update. The 3

sponsor assigned treatment arms that included Cenobamate and Phenytoin group, the Cenobamate and Phenobarbital group, the Cenobamate and Other Concomitant AEDs group were pooled to create a single arm of any patient treated with cenobamate. The JMP Clinical application was used for analysis. There were 1344 evaluated patients in this analysis pool. At the time of the 120-day safety update there were 1339 patients contained in the SDTM exposure dataset (EX.xpt). The mean and median daily dose for these patients was 177mg and 179mg respectively while the mean and median treatment durations were 352 and 355 days with a 1st quartile treatment duration of 271 days. In the C021 120-day safety update cohort there were 201 serious adverse events from 150 unique patients.

In the analysis of serious adverse events in study C021, the SOC's that have a frequency of 9 or more events will be examined by each SOC term in the subsequent paragraphs.

SOC

Nervous System Disorders

The highest frequency of SAEs occurred in the SOC "Nervous system disorders" with 64 events from 55 patients. The most frequent preferred terms within this group of events was "seizure" where there were 22 events from 22 patients (1.6%). There were no cenobamate discontinuations among these 22 events. Seizure SAEs occurred from study day 10 to 747 with a mean and median of day 205 and day 324 respectively. There is no clear temporal relationship to these seizure events, and these do not appear to indicate seizure worsening. This patient had additional preferred term entries for "jaw fracture", "concussion", "face injury", and "tooth fracture". Non-seizure related events were also prominent as seen in the evaluation of the pivotal studies in double blind phase and open label extensions. These events include "ataxia", "Dizziness", "somnolence", "dysarthria", "balance disorder". The majority of these events occurred in the 1st 8 months of cenobamate treatment.

Injury, Poisoning and Procedural Complications

The SOC with the second highest frequency of events (after "Nervous system disorders") was "Injury, poisoning and procedural complications". There were 29 events that occurred in 25 patients in this SOC. The most frequent preferred terms identified from this SOC were fractures. There were 17 preferred terms containing fracture from 15 patients. Overall treatment emergent (TEAE) adverse events from these 15 patients were examined for the co-occurrence of seizure, as a possible basis for the orthopedic injury. Among these 15 patients there were 119 TEAE entries. There was one patient with a preferred term entry for seizure. These events are identified as recovered with no change in cenobamate dose. The most common TEAE preferred term entries with a frequency greater than 2 were 7, 5, 4, 4, 3, and 3 instances of "somnolence", "dizziness", "headache", "fall", "upper respiratory tract infection", and "fatigue" respectively. The high co-association of central nervous system TEAE's "somnolence",

“dizziness” and “fatigue” are an indication that a portion of these injuries may be due to central nervous system dysfunction.

Infections and infestations

There were 23 entries from 20 patients in this SOC. The most frequent preferred term in this SOC is “appendicitis”. On inspection this event appears to be more frequent than commonly observed in a cohort of this size and duration of treatment in an antiepileptic drug trial. This adverse event will be examined further in the discussion of the preferred term frequencies and also in [Significant Adverse Events, 8.4.5 Appendicitis](#). There were 5 instances of pneumonia entered from 5 unique patients. The time to onset ranged from 4 days to 424 days where the median time to event was 161 days. All are entered as “recovered” while none of these “pneumonia” events resulted in treatment discontinuation.

From the remaining 12 adverse event preferred terms in this SOC from 10 patients there were 2 instances of urosepsis, 2 instances of urinary tract infection, one instance of sepsis, one instance of herpes zoster, two instances of gastroenteritis one instance of encephalitis, one abdominal wall abscess (this occurred in a patient with appendicitis), and one instance of cellulitis. From among these 12 adverse events, two patients had study drug discontinued, two had study treatment interrupted and in 6 patients cenobamate treatment was continued unchanged. Two of the adverse events were identified as “recovered/resolved with sequelae”. These events with sequelae were “encephalitis” and “herpes zoster”.

There was a preferred term “encephalitis” entered on study day 119 (patient (b) (6)). A lumbar puncture was performed. Serum glucose was depressed at 10mg/dl (corresponding serum glucose not provided) with a highly elevated protein of 600mg/dl. There is no report of microbiology from the 1st spinal fluid sample obtained 2 days after hospital admission. At the second lumbar puncture on the 6th day of hospital admission the narrative indicates “Chinese ink staining gene expert and bacteriologic culture were negative”. The patient’s clinical status was poor on discharge after a 17-day hospitalization. The patient was noted to be in a minimally conscious state, [see narrative](#). All laboratory values are examined during the study timeline. Absolute neutrophil count at baseline was $2.3 \times 10^9/L$ with a nadir of $1.1 \times 10^9/L$ on study day 60 that returned to baseline level at study day 88 but had some decline to $1.7 \times 10^9/L$ on study day 116. There were no other notable post baseline laboratory abnormalities.

The preferred term “herpes zoster” was entered on study day 296 (patient (b) (6)), [see narrative](#). This patient experienced a herpes zoster infection (shingles). The patient had a left facial shingles rash. The patient was subsequently hospitalized on study day 299 with a diagnosis of varicella zoster virus encephalitis and deranged liver function studies. The patient was treated with acyclovir 800mg three times a day, oxycodone 2.5mg twice a day as needed and pregabalin 25mg three times a day. The study drug was not changed due to the event. The patient was discharged home to continue intravenous acyclovir via PICC line. All laboratory values are

examined from the course of the 371-day study timeline. There was an episodic decline in absolute neutrophils from $2.7 \times 10^9/L$ at study day 115, however, the value at day 269, most proximate to the event of herpes zoster, the neutrophil value was $2.2 \times 10^9/L$. There was no consistent change from baseline to abnormal values of any laboratory metrics during the study timeline.

Figure 20 Study C021, Patient YKP3089C021- (b) (6) (*herpes zoster*), absolute neutrophil count during treatment with cenobamate.

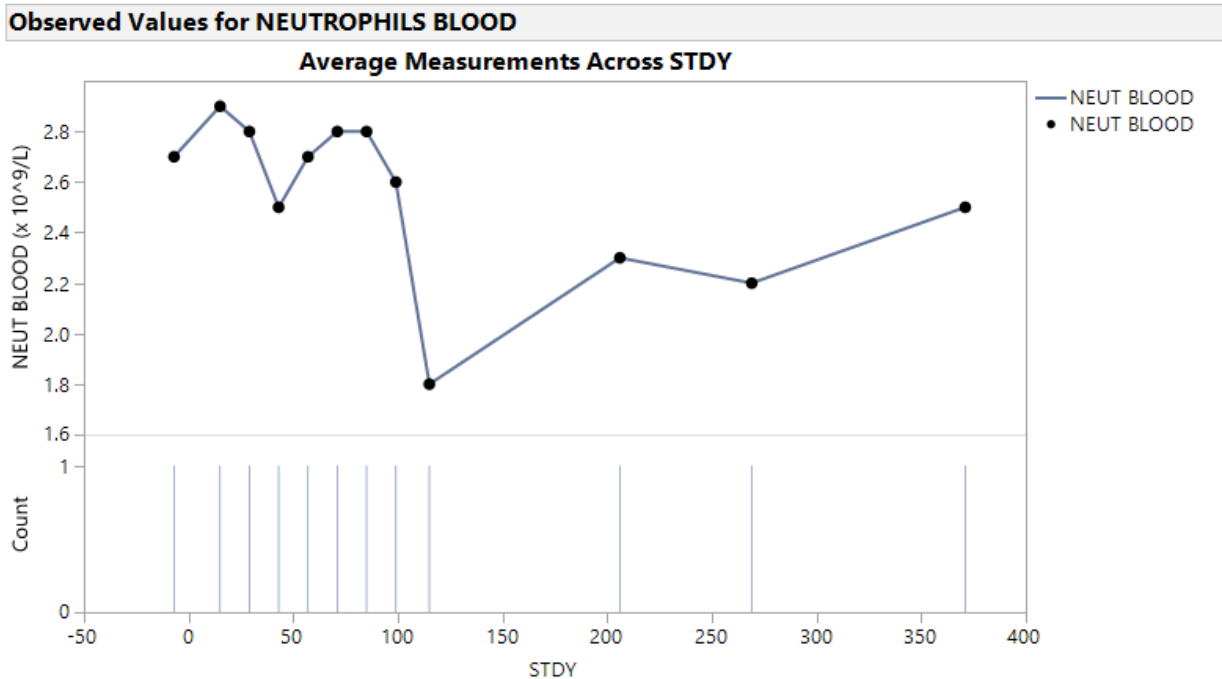
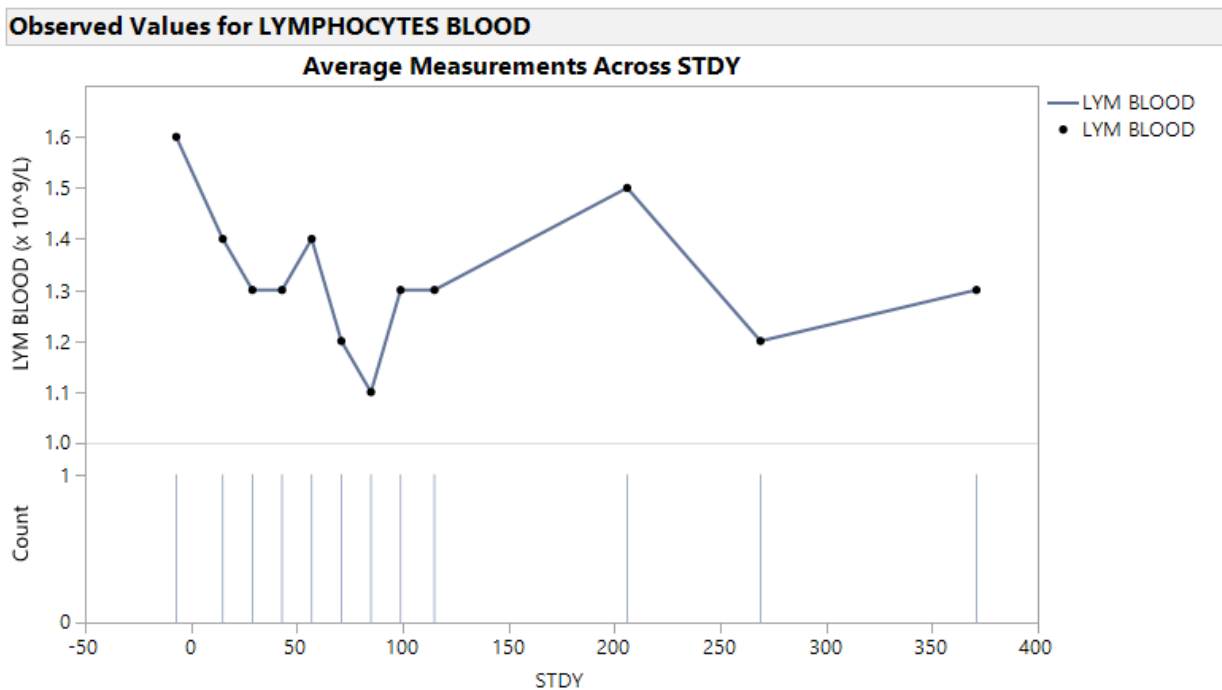


Figure 21 Study C021, Patient YKP3089C021- (b) (6) (*herpes zoster*), Lymphocyte count during treatment with cenobamate.



Reviewer Comment: There is an increase in appendicitis over expected background rate prompting evaluation of overall infection rate as well as the lymphocyte and neutrophil counts of patient YKP3089C021- (b) (6). The profile of events in the SOC “infections and infestations” does not appear to be high in relation to the size and medical status of the study population. The event of “encephalitis” is of uncertain etiology. There was a value of neutropenia, not critically low, that was not in temporal association with the diagnostic entry. It is not conclusive from the narrative that this was an infectious event. The profile of overall infectious event does not rise to a safety signal.

Psychiatric disorders

There were 17 entries from 16 patients in this SOC. The most frequent events were “suicide attempt” and “suicidal ideation”. These accounted for 6 events from 5 patients. The onset of these events ranged from study day 144 to 441 with a median of 189 days. One patient, YKP3089C021- (b) (6), is identified as having “recovered/resolved with sequelae”. The narrative for this patient’s event is examined and reveals an interval of psychosis preceded (*not entered as AE*) the suicide attempt. This patient was noted to have paranoid ideation from approximately study day 102 until the suicide attempt on study day 190. This event occurred 6 days after the last cenobamate dose. On study day 190 the patient stabbed himself multiple times. “The physical examination revealed approximately 10 abdominal stab wounds, 3 stab wounds on the right side of the neck, a 20cm long slash wound on the left forearm and a 5cm long slash wound on the right forearm. The CT procedure revealed liver injury as well as injury

of an abdominal vessel.” See [YKP3089C021-](#)^{(b) (6)} [narrative](#).

The next most frequent preferred term entry in this SOC is “mental status changes”. The earliest onset of a “mental status change” was on study day 79 with the latest on study day 330. The first patient ^{(b) (6)} discussed has an entry in the outcome variable (AEOU) of “recovered/resolved with sequelae”. The narrative report is examined. This report reveals that the patient’s spouse found the patient on the floor and noted her to be very unsteady. Gait continued to decline, and the patient was taken to the emergency room where recent memory was faulty. A CT angiogram was performed and did not reveal evidence of stroke. Right temporal encephalomalacia was identified. The narrative indicates the patient recovered from the altered mental status with sequelae 2 days after onset and from ataxia 9 days after onset. The reviewer conclusion is that this may have been a post-ictal event. The second report of mental status change was due to an acute alcohol intoxication. The third report of mental status change was ameliorated by a dose reduction from 200mg daily to 150mg daily.

The remaining 8 events in the “psychiatric disorders” SOC occur in 8 individual preferred terms. These preferred terms are “aggression”, “anxiety”, “depression”, “postictal psychosis”, “major depression”, “affective disorder”, “anxiety disorder”, and “psychotic disorder”. All are identified in the outcome variable (AEOU) as “RECOVERED/RESOLVED”. In three of the 8 events the study drug was discontinued. Two of these events occurred in the same patient.

Reviewer Comment: There is a signal for neuropsychiatric adverse effects based primarily on the frequency of suicidality. In the other terms from the “psychiatric disorders” SOC there were eight events. Three of these eight events may have a causal relationship based on temporal relationship. Two of these events were paranoid delusions where there was underlying psychiatric history in one case and in the second of the paranoid delusion cases an epileptogenic basis was possible. The third event was a “major depression” that was temporally related to cenobamate initiation but was managed while therapy continued for an additional 520 days.

Gastrointestinal disorders

There were 10 entries from 10 patients in this SOC. There were 3 entries of the preferred term vomiting and 2 with the preferred term abdominal pain. The remaining 5 terms were individual entries for constipation, enteritis, gastritis, lower gastrointestinal haemorrhage and pancreatitis chronic.

Reviewer Comment: From among the gastrointestinal events obstipation may have a causal relationship supported by the high frequency of “constipation” adverse events in the clinical trials. Among the remaining serious adverse events a relationship to cenobamate is not adequately supported.

Skin and subcutaneous tissue disorders

There were 9 entries from 9 patients in this SOC. The most frequent event preferred term was “rash Papular” with 3 entries. The remaining six entries was from six distinct preferred terms. All nine events were reported resolved in the AEOUT variable while cenobamate was discontinued in 8 of the 9 patients.

Reviewer Comment: All of the SAEs in this category were based in a hypersensitivity responses. Examination of these SAEs reveals that development of these hypersensitivity reactions usually occurs within 60 days of the start of cenobamate. There were two cases of “rash papular” without a temporal relationship. There was one case with a rash onset on day 316 and a second with rash onset at day 138. These SAEs are consistent with the strong hypersensitivity signal that has been observed in cenobamate treatment.

Terms of Interest from SOC’s with Less than 9 Entries

There were 16 SOC’s that had less than 9 entries. Among these there were 49 entries containing 44 preferred terms from 39 patients. Individual reports from entries will be examined where the event is identified as “resolved with sequelae” in the AEOUT variable or where cenobamate was withdrawn identified in the AEACN or the event is identified as severe in the AESEV variable. Nineteen entries from 16 patients fulfil these criteria.

There remain 22 entries from 20 patients that do not fulfill criteria for narrative inclusion based on the specific variable (AEACN, AEREL, AEOUT) criteria described above. From this group, selected terms of interest that may be related to hypersensitivity, are unexpected, and potentially highly threatening are chosen for examination. These events will include: “visual acuity reduced”, “Acute myocardial infarction”, “pyrexia”, Fibrin D dimer increased”, “acute kidney injury”, “acute respiratory failure”, “breast cancer” and “deep vein thrombosis”.

Less than 9 entries with Outcome “Resolved with sequelae”

Reviewer Comment: among these reports there was a report of a pulmonary embolism and a report of deep venous thrombosis without alternative cause. There was however, no temporal relationship where both occurred after more than six months of exposure. The remaining events in this group had no causal relationship or were in a category where causality could not be excluded but were isolated events without a comparator placebo arm. Condensed summaries of the case narratives are presented in [Appendices 13, 13.2.1 Summaries From the Category of “Less than 9 entries with Outcome ‘Resolved with sequelae’”](#)

Reports not Captured by Variable “AEACN, “AEREL” and “AEOUT” Criteria.

There were 30 entries from 25 patient containing 28 preferred terms that did not fulfill capture

criteria based on the “AEACN, “AEREL” and “AEOUT” variables described in the section above: [Terms of Interest from SOC’s with Less than 9 Entries](#). From this remaining group of serious adverse events there are eight preferred terms of interest selected. These terms are selected to have a narrative summary entry due to the potential they represent for a high physiologic threat or potential relationship to DRESS. These eight preferred terms include “Acute kidney injury”, “Acute myocardial infarction”, “Acute respiratory failure”, “Breast cancer”, “Fibrin D dimer increased”, “Pyrexia”, “Tetany”, and “Visual acuity reduced” captured from 6 patients.

Reviewer Comment: from among this category of reports there were clear causally related events. One event of concern is a myocardial infarction that occurred in a 38-year-old female. The earliest symptoms were at treatment day 80 although the infarct occurred at study day 170. This event is confounded by a history of dyslipidemia and a light smoking history as well as a family history of cardiovascular disease. The patient’s mother had a myocardial infarction at age 50. The attribution of this event is not adequate to influence approvability or add to labeling. A condensed version of the narrative summaries may be seen in [Appendices 13 Reports \(of interest\) not Captured by Variable “AEACN, “AEREL” and “AEOUT” Criteria](#).

Exploration of Selected Preferred Terms

The term “appendicitis” was identified in 6 entries from six patients (0.5%) in study C021. Cenobamate exposure in study C021 at the time if these entries is calculated as approximately 1394 patient years. The occurrence of 6 cases of appendicitis yields an incidence of 4.3/1000 patient years of exposure. This is greater than the reported background incidence of 1.1/1000 population per year.¹⁰ This adverse event will be explored further in Section 8.4.5, [Appendicitis](#).

8.4.3. SAE, Summary and Conclusions

Reviewer Comment: Analysis of serious adverse events in the double-blind period reveals a higher frequency in the cenobamate treatment arms but without a clear dose response relationship. The most frequent adverse events in the placebo arm are events related to epilepsy with seizure terms almost equally divided between placebo and treatment arms. There was a minimum of epilepsy terms in the 400mg arm. “Nervous System Disorder” events that predominate in the cenobamate treatment arm are related to central nervous system dysfunction, suicidality, and drug hypersensitivity. The safety events to consider for labeling are central nervous system adverse events, drug hypersensitivity and suicidality. These are present in proposed labeling. The single event of ALT elevation, entered as an SAE, reached a maximum of 7.6 x ULN while on 400mg cenobamate. The ALT value improved to 2 x ULN 12 days after study drug discontinuation. A single event of “pulmonary embolism” occurred in the 100mg

¹⁰ 1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. THE EPIDEMIOLOGY OF APPENDICITIS AND APPENDECTOMY IN THE UNITED-STATES. *American Journal of Epidemiology* 1990;**132**(5):910-25 doi: 10.1093/oxfordjournals.aje.a115734[published Online First: Epub Date]].

cenobamate treatment arm associated with a cerebral infarction. This event may have been related to change in physical activity.

In the open label extension of the pivotal trials C013 and C017 20 events of epilepsy were distributed across a long exposure timeline without clustering early or late in treatment. This points away from both pro-convulsant and loss of efficacy distribution patterns. There were 3 patients with a myocardial infarction where the events occurred on average 2.7 years after starting cenobamate. Two patients had plausible cardiovascular risk factors. Given the high background rate of myocardial infarction a causal relationship is not supported for these events. Two patients had cerebrovascular events (stroke) with a temporal relationship to initiation of cenobamate treatment, although both patients had a history of cerebrovascular disease. The temporal relationship does support potential causality in a circumstance of selective vulnerability. In this OLE safety dataset there were two cases of interest where elements of central nervous system dysfunction, usually associated with the earlier treatment period, occurred as “balance disorder” and “vertigo” on days 1192 and 377 respectively. Symptoms were ameliorated by dose reduction, demonstrating a dechallenge response. Two severe psychiatric events of psychosis were identified, in one case there was causal support based on a dechallenge response while in the second there is no causal support and the event resolved spontaneously without change in cenobamate dose. These events raise a concern for an adverse psychoactive property of cenobamate but do not provide conclusive support.

Examination of serious adverse events in the open label study C021 reveals the highest frequency of events in the “nervous system disorders” SOC. Seizure related events were the most frequent followed by central nervous system dysfunction. The severity of these later events was judged as “moderate” or “severe” in the majority of cases but there were no cenobamate discontinuations. There was a higher frequency of seizure related events in the 1st 60 days but thereafter a more event distribution to 420 days. This distribution, as in the discussion of epilepsy related events in the pivotal open label studies does not raise alarm for seizure worsening or lack of efficacy but is consistent with an ongoing background rate of seizures in a refractory population. The “injury, poisoning and procedures” SOC contained 3 “fall” events. Two of three falls occurred in the first 2 months and the third at near 6 months. The “infections and infestations” SOC contained an unexpected high frequency of the preferred term “appendicitis”. Exploration of the development program identified 9 cases of appendicitis that yields an estimate for a frequency that is 2.6-fold greater than the expected background rate, see [Significant Adverse Events 8.4.5, Appendicitis](#). The “psychiatric disorders” SOC revealed 5 patients had an entry of suicide attempt or suicidal ideation. This yields an occurrence of 3.7 events per 1000 patients that is similar to the signal of 3.4/1000 patients for suicidality in current class labeling for Antiepilepsy drugs. There were two events of psychosis. In one case the psychosis preceded a suicide attempt. This indicates a possible signal for an adverse psychoactive effect of cenobamate. Examination of serious adverse events in the “gastrointestinal disorders” SOC did not reveal notable safety signal. Examination of the “skin and subcutaneous disorders” SOC revealed 9 serious adverse events from 9 patients. Of note, 7 of the 9 events occurred in the 1st 90 days. There were 2 SAEs that developed rapidly after

initiation of cenobamate. In the 1st case the SAE entry entered as “swelling face” (ID YKP3089C021- (b) (6)) developed on day 2 of treatment with cenobamate 12.5mg. In this second rapid onset case a patient developed an urticarial body rash after the 2nd dose of 12.5mg cenobamate (YKP3089C021- (b) (6)). These reports demonstrate the high potential for a hypersensitivity response with cenobamate treatment. Seven of the 9 events led to cenobamate discontinuation. The high rate of discontinuation is in alignment with heightened pharmacovigilance in the study for hypersensitivity reactions. No new cases of DRESS occurred in study C021. There was an event of myocardial infarction in a 38 year old female. This event is confounded by an early family history of cardiovascular disease and a comorbidity of a hyperlipidemia syndrome. However, the young age of the patient involved is a potential cardiovascular safety signal, possibly for patients with an underlying vulnerability such as strong family history.

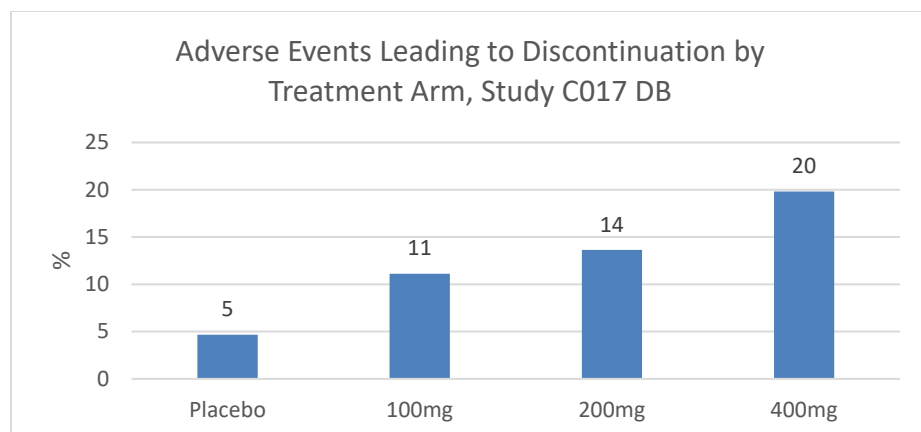
Conclusion: Examination of serious adverse events in the phase 2/3 safety datasets reveal the core safety issues are central nervous system dysfunction that may be severe but generally occur early after initiation of cenobamate. The reduced titration rate may mitigate this effect, although there were reports of these SAE events after long periods of exposure. The next major core safety issue are psychiatric disorders where suicidality frequency is in alignment with the current AED class labeling. There were four reports of psychotic disorder that indicate a signal for an adverse psychoactive effect of cenobamate. There were reports of appendicitis with a frequency higher than expected background rate. Hypersensitivity reactions were evident and could emerge very early after the start of cenobamate exposure. There was a case of DRESS in study C017 but no new DRESS cases were identified in study C021 at the reduced cenobamate titration rate, see [DRESS Risk, 8.6.1](#).

8.4.4. Dropouts and/or Discontinuations Due to Adverse Effects

C017

There were 8 (4%), 12 (11%), 20 (9%), and 22 (20%) patients in the Placebo, 100mg, 200mg, and 400mg treatment arms respectively that had adverse events leading to discontinuation. There is a dose response for discontinuation seen, [Figure 22](#). Discussion of the instances of adverse events leading to discontinuation will be captured in the following section C013-C017 Pool that will cover discontinuations in the pooled pivotal study double blind dataset.

Figure 22 Study C017 Adverse Events Leading to Discontinuation by Treatment Arm by Percent of Dose Group



C013- C017 Pool

There were 82 adverse events from 66 patients leading to cenobamate discontinuations. From among these patients there were 8 (4%), 12 (11%), 20 (9%), and 22 (20%) in the Placebo, 100mg, 200mg, and 400mg treatment arms respectively that had adverse events leading to discontinuation. There is not a clear dose response, but the highest rate of discontinuation was in the 400mg treatment arm, [Figure 23](#). When discontinuation by treatment arm is examined from study C017 alone without the pooled placebo and 200mg treatment arms from study C013 there is a dose response for adverse event related discontinuations, [Figure 22](#).

There was one patient with six treatment emergent adverse events with an identification as “drug withdrawn” in the AEACN variable, one patient with 3 events linked to “drug withdrawn” and 7 patients with 2 adverse events linked to “drug withdrawn”. The remaining 52 patients each had one adverse event associated with “drug withdrawn”.

There were 17 events from 16 patients where the investigator severity entry is “severe” and from among these there were 3 events from three patients identified as definitely related. The preferred term of these events were “lethargy”, “somnolence” and “vertigo”. There were 7 events from 7 patients with a relatedness entry of “probable”. The preferred terms for these events were “erythema”, “drug reaction with eosinophilia and systemic symptoms” (DRESS), “cognitive disorder”, “fatigue”, “somnolence” and 2 entries of “ataxia”. From among all of these “severe” events all but one had an outcome entry of “recovered/resolved”. In the case of DRESS, the outcome is entered as unknown. This case is presented in the following paragraph.

DRESS

YKP3089C017- (b) (6) (PT DRESS):

36-year-old white female. On study day 24 the subject presented to an emergency room with a several day history of fever and chills; a 2-day history of diffuse macular erythematous and pruritic rash covering the majority of body surface area including the face, trunk, back, arms, and legs; headache; arthralgia; myalgia; and memory problems. The patient was hospitalized, upon admission, the subject had a fever with temperature of 101.3°F and a morbilliform rash on the abdomen and legs. The last entered site visit is study day 11 while the final study laboratory day -2. Laboratory studies related to the DRESS event are obtained from the hospitalization and reveal elevation of ALT that reached a maximum of 117 (approximately 3.5 x ULN of the study upper range), eosinophil percent increased to 15.3%, and platelet count reached a nadir or 142,000, within normal study reference range. Note, hospital reference ranges are not provided.

During hospitalization a CT scan of the chest and pelvis was performed on study day 29 to evaluate for lymphoma. Findings included bilateral pleural effusion, right side was greater than the left side, with right lower lobe consolidation. A moderate amount of free fluid in the abdomen and pelvis tracking along the right pericolic gutter was observed, with either a thickened gallbladder wall versus fluid in the gallbladder fossa. Mediastinal lymph nodes were enlarged bilaterally but not consistent with lymphoma along with bilateral axillary and inguinal lymph nodes. The subject was treated with methylprednisolone (60 mg, IV, every 8 hours) before being transitioned to prednisone but duration of this treatment is not reported. On study day 31 the patient was discharged from the hospital but returned to an emergency room on study day 35 and 38 due to rash. Following this, the subject was lost to follow up despite multiple attempts to have her return with a conclusion of DRESS outcome unknown.

Cenobamate dose: the last recorded dose in the exposure dataset is entered on study day 7. The study narrative indicates no study drug was taken from study day 8 to 12. The patient was scheduled to escalate dose from 100mg to 200mg on study day 8 and the investigator indicates the last dose of study drug was 200mg on study day 16 (although not verified in exposure dataset).

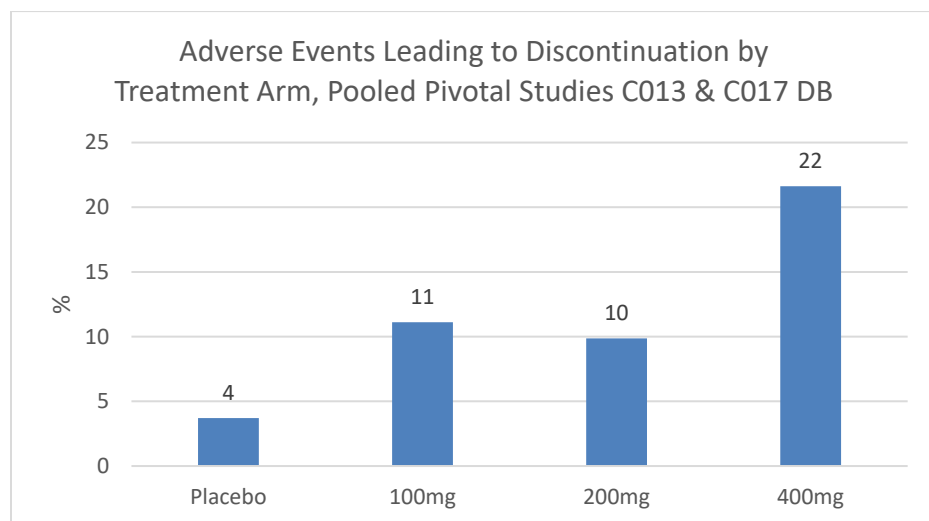
Table 25 YKP3089C017- (b) (6) (PT DRESS), Core Laboratory Values by Study Day at Baseline and During DRESS Hospitalization.

study Day	Study visit	Hospitalization*		
	-2	23	26	27
ALT (10-33)	10	81		117
AST (10-36)	16	54		158
Eosinophil %	1.5	13.6		15.3
HB (11-15.5)	13.1	13.3		10.1
Lymphocyte %	33	16.6		16.8
Neutrophil %	59	59		64

Platelet count x 10 ³	229	142		169
Serum Na	138	132		
WBC	6.6	4	3.8	5.3
Hospital reference ranges not provided, values in lab test are study normal range				

Causal Assessment: The patient presents to an emergency room on study day 24 with fever and rash. Last onset contact was study day (-2) and prior phone contact was study day 18 where “tiredness” is reported but no other abnormal finding. The temporal profile of cenobamate intake is incomplete with the last confirmed dose of 100mg on study day 7. It is unclear if any further cenobamate treatment followed. The event therefor may have occurred 17 days after last cenobamate although this is uncertain. The temporal relationship to cenobamate treatment and absence of reported introduction of confounding medications in the same timeframe essentially confirm causal relation to cenobamate. The event had serious multiorgan effects including mediastinal adenopathy, serositis, fever and increased eosinophils. Rash also persisted after hospital discharge and resolution is not confirmed due to “lost to follow up”.

Figure 23 Study C017 Adverse Events Leading to Discontinuation by Treatment Arm by Percent of Dose Group



The preferred terms associated with discontinuation at a frequency greater than one patient in any dose group were “Ataxia”, “Dizziness”, “Somnolence”, “Nystagmus”, “Vertigo” and “Diplopia”. A composite group of All Rash that included “Rash, Rash Macular and Rash Pruritic” was also in this frequency category. These discontinuations are seen in [Table 26](#). The “All Rash” summation category did not have a dose response.

Table 26 C013- C017 DB Pool, Adverse Events leading to Discontinuation by Dose Group

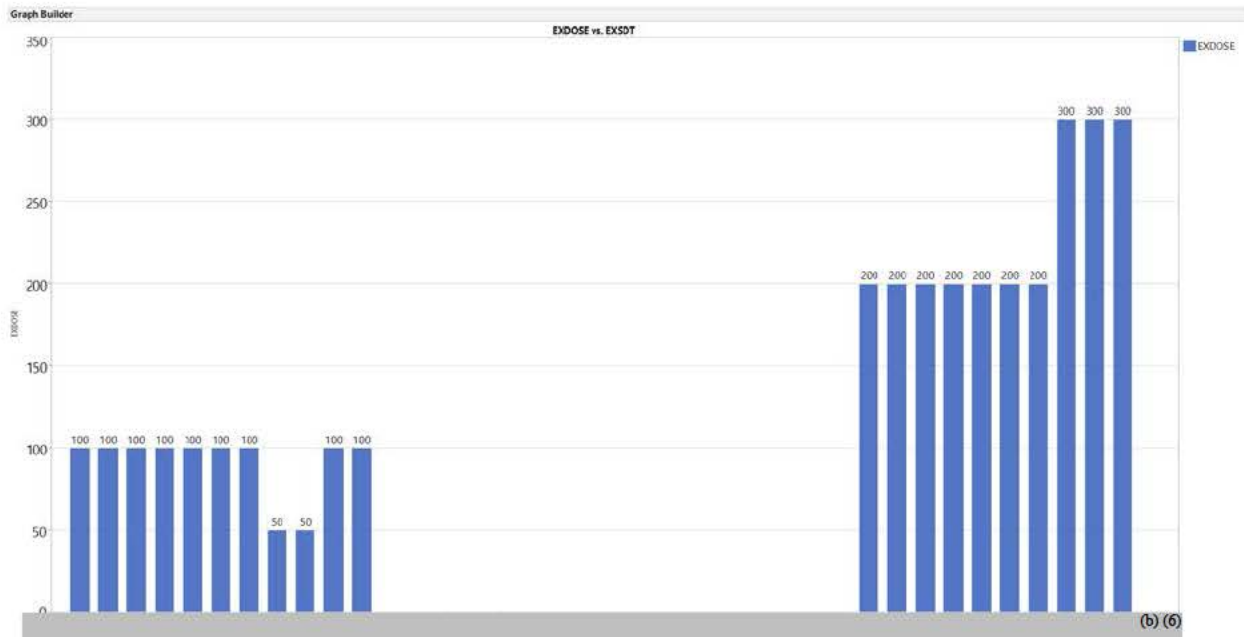
Preferred Term	Placebo	100 mg	200 mg	400 mg	% placebo	% 100mg	% 200mg	% 400mg
ATAXIA	1	0	3	4	0.5	0.0	1.3	3.6
DIZZINESS	1	0	3	4	0.5	0.0	1.3	3.6
SOMNOLENCE	1	1	1	4	0.5	0.9	0.4	3.6
NYSTAGMUS	0	0	1	2	0.0	0.0	0.4	1.8
VERTIGO	0	0	1	2	0.0	0.0	0.4	1.8
DIPLOPIA	0	0	0	2	0.0	0.0	0.0	1.8
All Rash (PT, Rash, Rash Macular, Rash Pruritic)	1	1	2	1	0.5	0.9	0.9	0.9

Ataxia

The narratives of 3 patients with the preferred term “Ataxia” are examined to assess the severity of the adverse events, concomitant medications and titration rate.

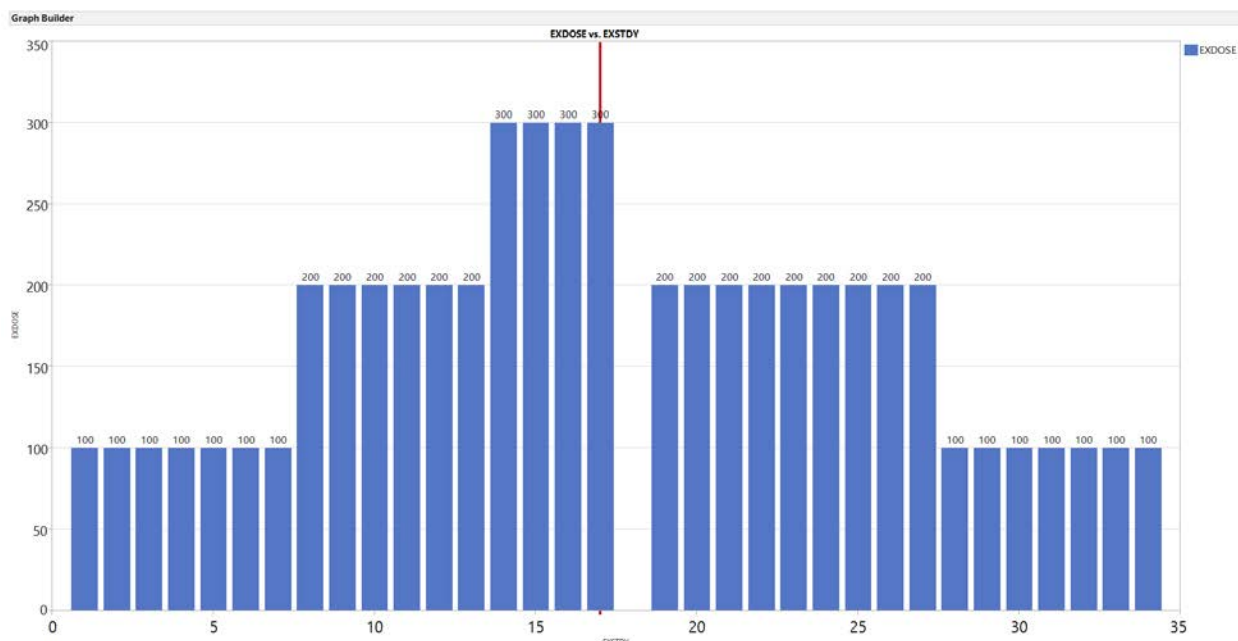
YKP3089C017- (b) (6) (PT Ataxia): 43-year-old white male experienced severe SAEs of nystagmus, ataxia, and dizziness on study day 42. the subject arrived at the medical center with suspected drug intoxication and was admitted to the hospital. The subject complained of dizziness, nystagmus observed when looking sideways, and truncal ataxia. abnormal general movement, gait, biceps, finger-nose, heel-shin (hemiataxia), knee, rapid alternating movements, and Romberg’s tests secondary to left hemiparesis (present in medical history) and nystagmus with gaze evoked bilateral and truncal ataxia. Cenobamate was discontinued. The patient had been escalated to a cenobamate dose of 300mg on study day 35 and titration was started at 100mg on day 0. There is an interval between study days 10 and 28 with no entries in the exposure dataset, [Figure 24](#). It is unclear if medication was not received. Concomitant medication included clonazepam 15mg BID and lamotrigine 350mg BID. *Causal assessment: This event was in temporal proximity to a 100mg dose increment precede the event by 4 days. The close relationship to dose escalation support a causal relationship. In addition, the event appears to be a notable CNS intoxication characteristics. There was underlying CNS vulnerability based on the medical history of a left hemiparesis and mild cognitive impairment. The medical history is brief so a detailed assessment of the degree of compromise is uncertain.*

Figure 24 Patient YKP3089C017- (b) (6) Dose by Date



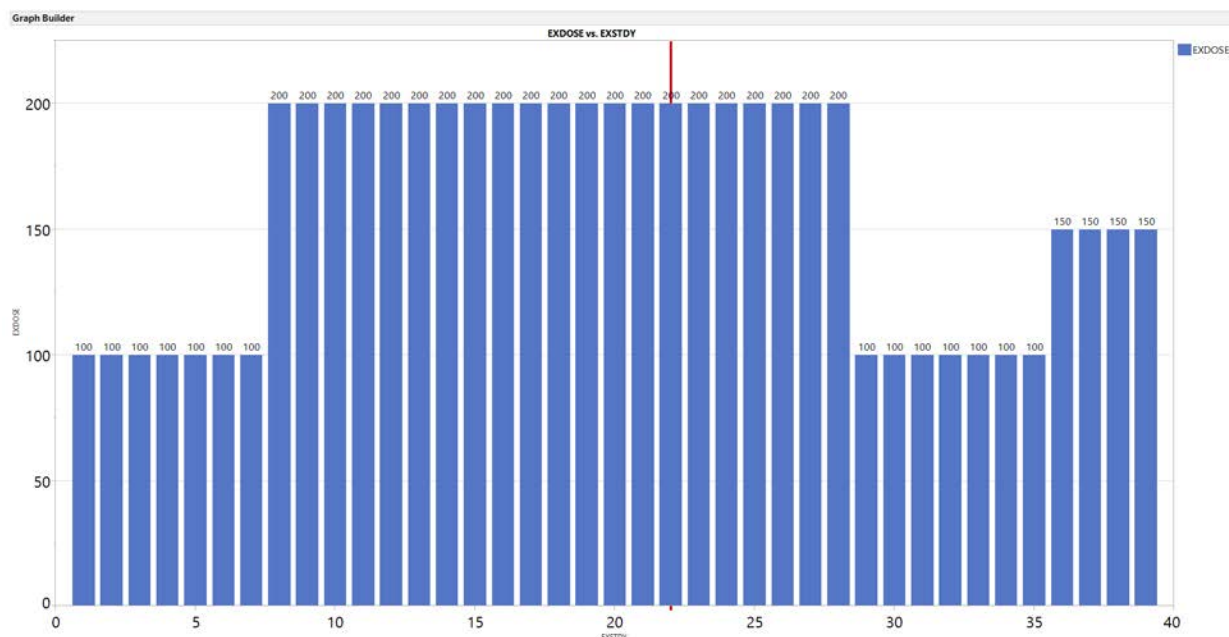
YKP3089C017- (b) (6) (PT Ataxia): 55-year-old white female Study Day 17, the subject experienced mild AEs of ataxia and nystagmus. The study drug was withdrawn due to the events and the last dose was taken on study day 17, see Figure 25 (ADEX dataset identifies last dose on day 33). A neurological examination on the same day showed the following significant abnormal findings: gait with mild ataxia and Romberg's test showing instability; the clinically significant abnormal finding included horizontal nystagmus on the left eye. At the time of the events of ataxia and nystagmus, the subject also experienced nonserious AEs of vision blurred, vomiting, and nausea. Concomitant Antiepilepsy drug was carbamazepine. *Causal Assessment: The events of ataxia, nystagmus, vomiting, and nausea occurred on the 4 day following dose escalation from 200mg to 300mg. This temporal relationship supports causality. The OCP review indicates that carbamazepine increases the oral clearance of cenobamate by 15% in population PK modeling. This event is not due to interaction with carbamazepine based on modeling of clearance.*

Figure 25 Patient YKP3089C017- (b) (6) Dose by Study Day (Red Line = Discontinuation)



YKP3089C017- (b) (6) (PT Ataxia): 44-year-old white male On Study Day 22), [Figure 26](#), the subject experienced a mild AE of ataxia. On study day 29, a neurological examination showed the following clinically significant abnormal findings: gait with mild sway and unsteady but can walk in tandem and nystagmus, which was unspecified in examination per source. The study drug was withdrawn due to the event and the last dose was taken on study day 39. Concomitant AED medications included clobazam (20 mg, oral, QD), topiramate (50 mg, oral, QD; 100 mg, oral, QD), and lacosamide (200 mg, oral, BID). A population PK modeling study. Causal Assessment: This adverse event occurred 15 days after dose escalation from 100mg to 200mg cenobamate, during the phase of escalating concentration and is consistent with the adverse CNS effect profile of cenobamate, [Figure 4](#). Causality is likely. Concomitant clobazam decreases oral clearance of cenobamate by 19% in a Population PK study noted in the OCP review. This decrease may have contributed to the adverse effect.

Figure 26 Patient YKP3089C017- (b) (6) (PT Ataxia) Dose by Study Day (Red Line = Discontinuation)

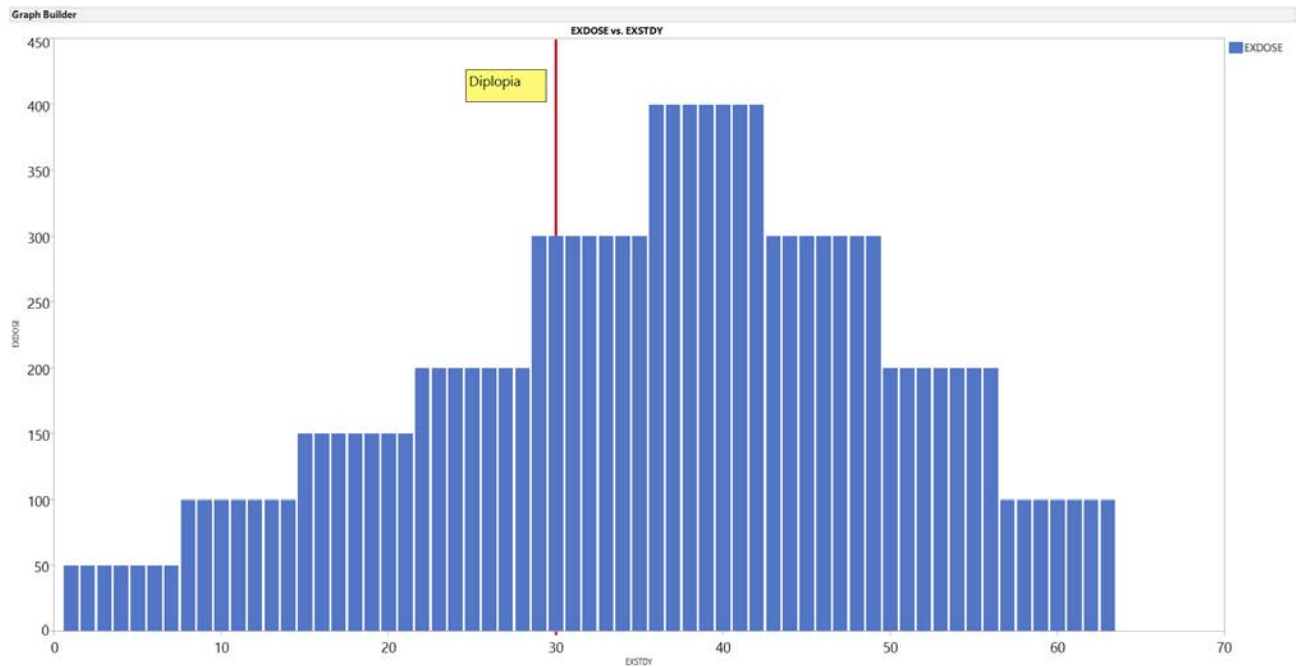


Reviewer Comment: the adverse event of “ataxia” leading to discontinuation is plausibly related to cenobamate in the 3 discontinuations that were examined. In all three reports that event occurred either proximal to a dose escalation or during the phase of rapid escalation of plasma cenobamate level. Discontinuations due to ataxia were more frequent in cenobamate treatment than in the placebo with 88% in the cenobamate treatment arm. There were 17 “ataxia” adverse events from 16 patients in studies C013 and C017 on cenobamate treatment where it is observed that 82% of these events occurred in the 1st 6 weeks of treatment.

Diplopia

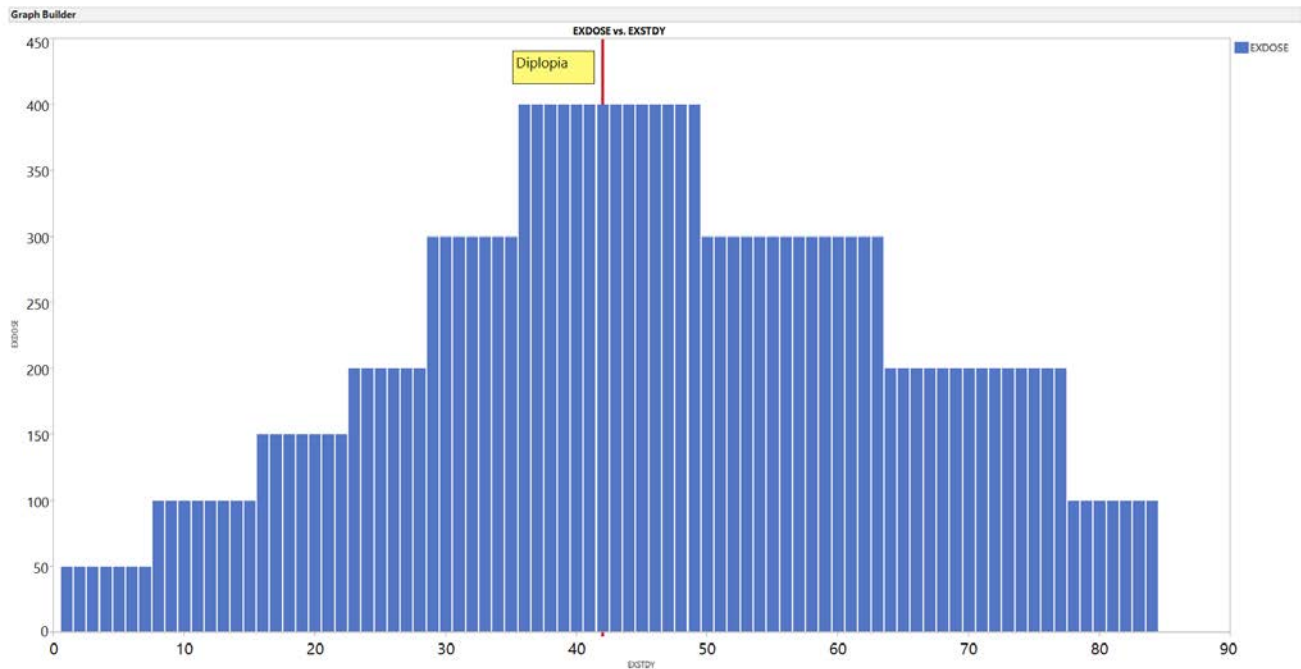
YKP3089C017- (b) (6) (PT Diplopia): 26-year-old white male (Study Day 30), the subject experienced a moderate AE of diplopia on study day 30. The patient also had some slowing of rapid alternating movements on neurologic exam. The patient was assigned to the 400mg treatment arm. The event of diplopia occurred on the second day of escalation to 300mg. Study drug was discontinued on study day 62. Concomitant AEDs included oxcarbazepine (600mg-900mg), valproate (800mg-1000mg). Causal assessment: This event occurred just following a dose escalation. *The temporal relationship to dose escalation supports a causal association. The patient is in the titration phase where there is a steep increase in plasma cenobamate concentration, (see Clinical Pharmacology, Figure 4 and Figure 27).*

Figure 27 YKP3089C017- (b) (6) PT Diplopia, Dose by Study Day



YKP3089C017- (b) (6) (PT Diplopia): 39 yo Caucasian female developed diplopia on study day 39. On study day 42 a neurologic exam revealed bilateral dysmetria, gait deviated towards the left side, horizontal and bilateral nystagmus with diplopia, and truncal ataxia towards the left side and backward. No pre-existing focal neurologic deficit is present in the medical history. Concomitant AEDs include levetiracetam (1000 mg, oral, BID; 500 mg, oral, BID) and valproic acid (500 mg, oral, BID). The patient was discontinued from the study on day 49 with subsequent resolution of the diplopia. *Causal assessment: This event occurred during dose escalation in the phase of rapid increase in plasma cenobamate level. This event is likely causal to this rapid elevation in cenobamate concentration, see Clinical Pharmacology, Figure 4 Error! Reference source not found. and Figure 28, cenobamate dose by day.*

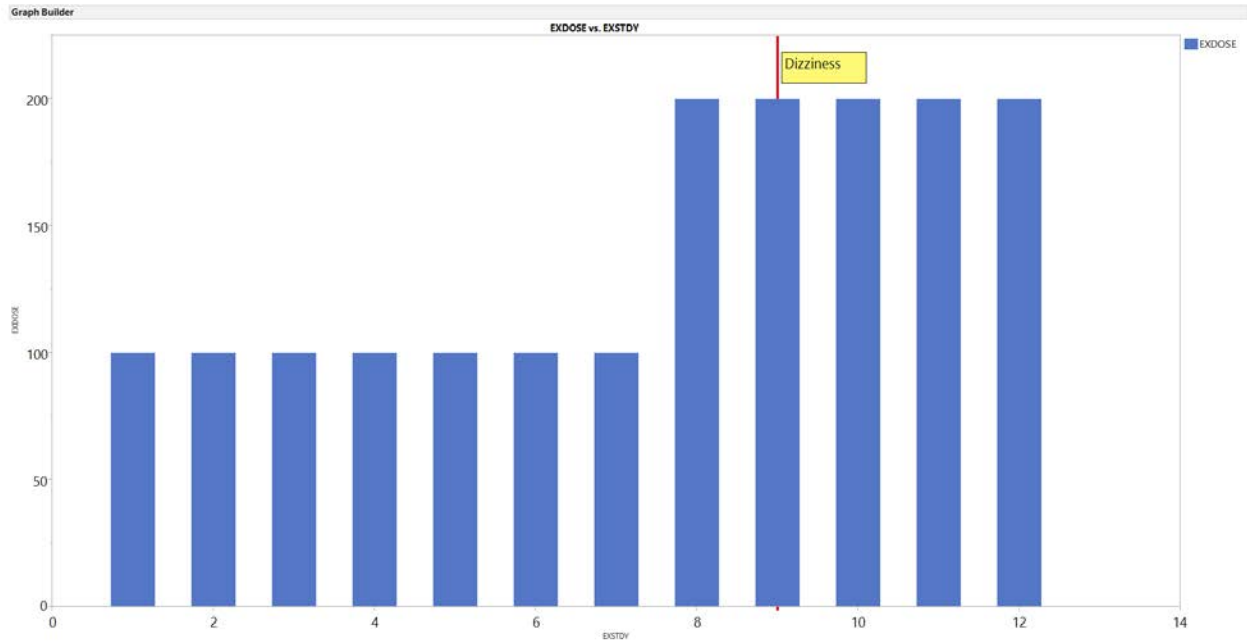
Figure 28 YKP3089C017- (b) (6) (PT Diplopia), Cenobamate Dose by Study Day



Dizziness

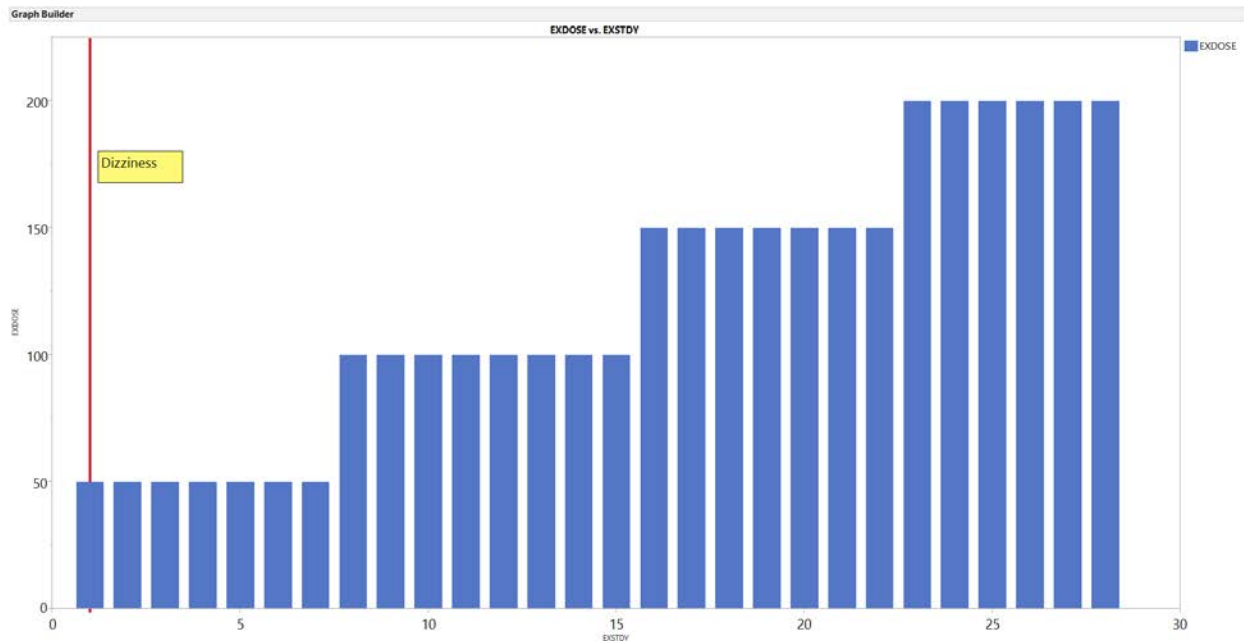
YKP3089C017- (b) (6) (PT Dizziness): 49-year-old Asian male the subject was randomly assigned to YKP3089 200 mg and began titration with 100mg cenobamate on study day 2. Medical history included mitral valve replacement, benign prostate hypertrophy, brain hemorrhage, stroke, and depression. Ongoing medical conditions included hypertension, sinus bradycardia, high cholesterol, brisk reflexes left arm and leg, hemiparetic gait, left hemiparesis, and spasticity left arm and leg. Concomitant AED medication included lacosamide 500 mg, oral, BID). On Study Day 9, the subject experienced a mild AE of dizziness. No treatment was reported for the event. The study drug was withdrawn due to the event and the last dose was taken on study day 12. *Causal assessment: This event of dizziness occurred on day 2 following escalation from 100mg to 200mg cenobamate. This is likely causally associated with the rapidly increasing plasma cenobamate see Figure 4 and Figure 29.*

Figure 29 YKP3089C017- (b) (6) PT Dizziness, Cenobamate dose by Study Day



YKP3089C017- (b) (6) (PT Dizziness): 26-year-old white male assigned to the cenobamate 400mg treatment arm developed dizziness on study day 1 and discontinued from the study. The narrative also reveals the patient experienced headache. Although the event occurred on day one the patient continued cenobamate treatment until day 12, Figure 30. *Causal assessment: This event during titration is commensurate with the rapid titration rate beginning with 100mg cenobamate.*

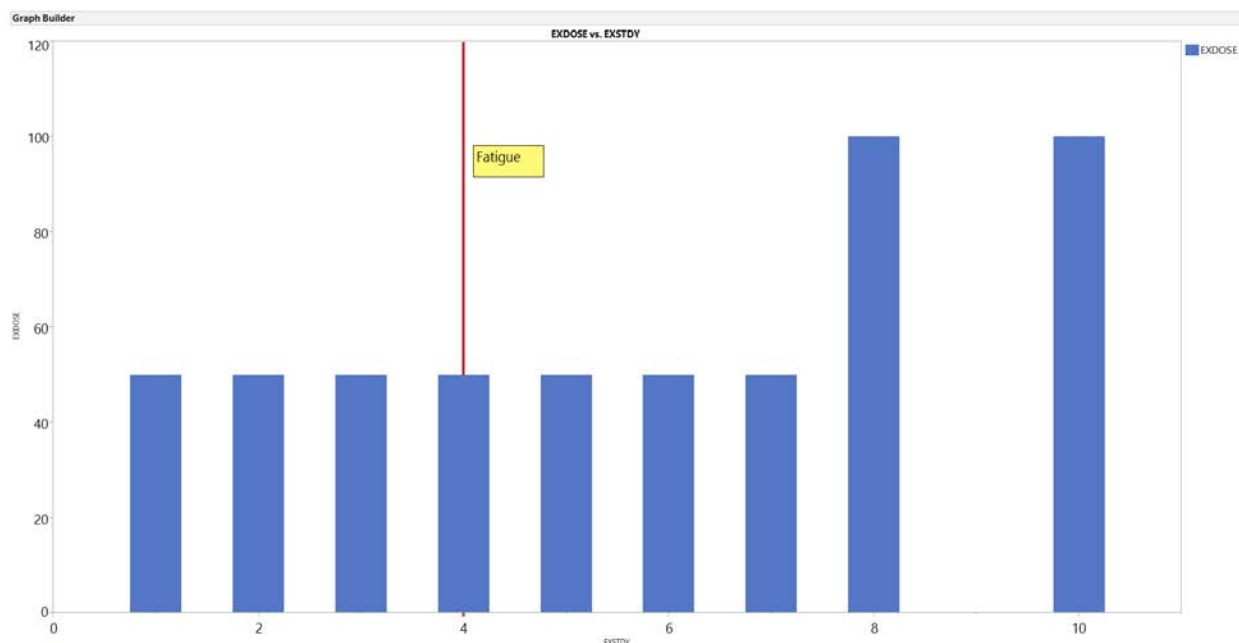
Figure 30 YKP3089C017- (b) (6) (PT Dizziness), Cenobamate dose by Study Day



Fatigue

YKP3089C017- (b) (6) (PT Fatigue): 45-year-old white male developed fatigue on study day 4. This patient began titration at 50mg daily and did reach 100mg a day on study day 8. Last day of cenobamate was study day 10. Ongoing medical condition included back pain. Concomitant AED medications included lamotrigine (250 mg, oral, QD) and sodium valproate (500 mg, oral, BID). *Causal Assessment: The event is causal to intolerance during early titration.*

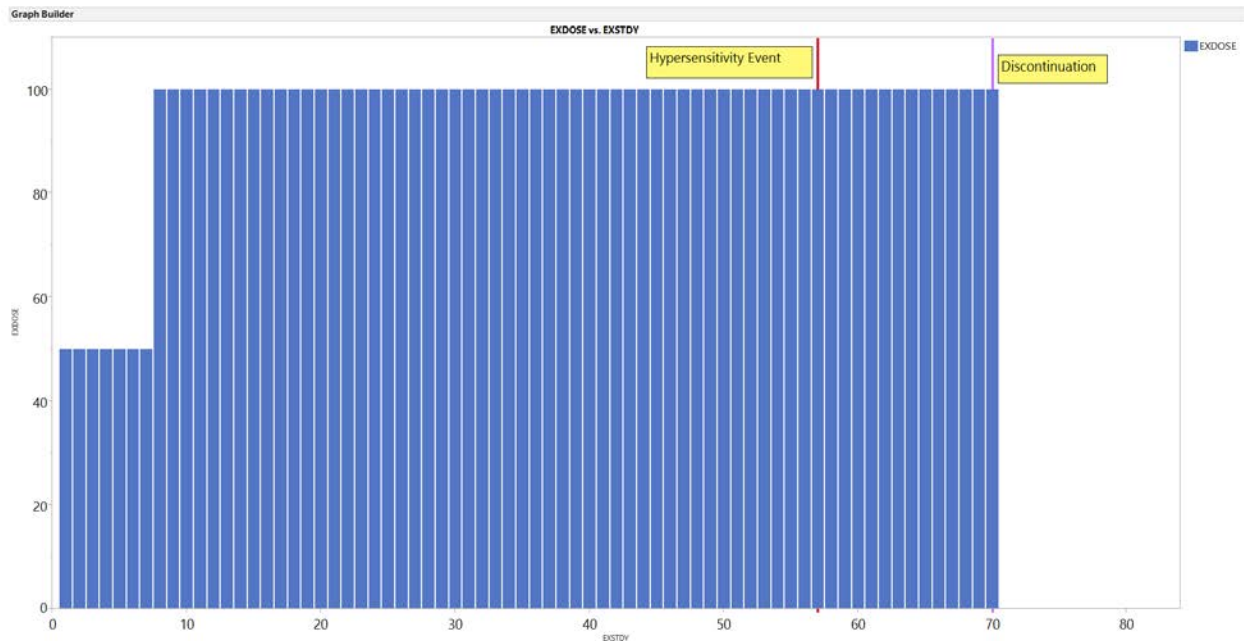
Figure 31 YKP3089C017- (b) (6) (PT Fatigue), Cenobamate dose by Study Day



Hypersensitivity

YKP3089C017- (b) (6) (PT Hypersensitivity): This report is explored because it was the single discontinuation due to hypersensitivity in the DB pivotal study pool. The patient was randomized to a daily dose of cenobamate 100mg/day and began titration phase at a dose of 50mg daily x 1 week (reduced titration rate of protocol amendment 1/7/2014). On Study Day 57, the patient experienced a moderate AE of hypersensitivity (verbatim term: allergic reaction with rash and swelling of the face). The patient was treated with hydroxyzine dihydrochloride (10 mg, oral, every 12 hours) and levocetirizine (5 mg, oral, every 24 hours). The study drug was withdrawn due to the event and the last dose was taken on study day 70. On study day 88, the outcome of the event of hypersensitivity was recovered/resolved. The CRF and patient profile are examined but no additional clinical detail concerning the clinical course of pruritus, rash or swelling are provided). The profile of cenobamate exposure is shown in [Figure 32](#). *Causal Assessment: The event is in alignment with the hypersensitivity potential of cenobamate. This event was delayed to day 57. There was apparently successful treatment with antihistamines only and a report of resolution 18 days after study drug discontinuation.*

Figure 32 YKP3089C017- (b) (6) (PT Hypersensitivity), Cenobamate dose by Study Day

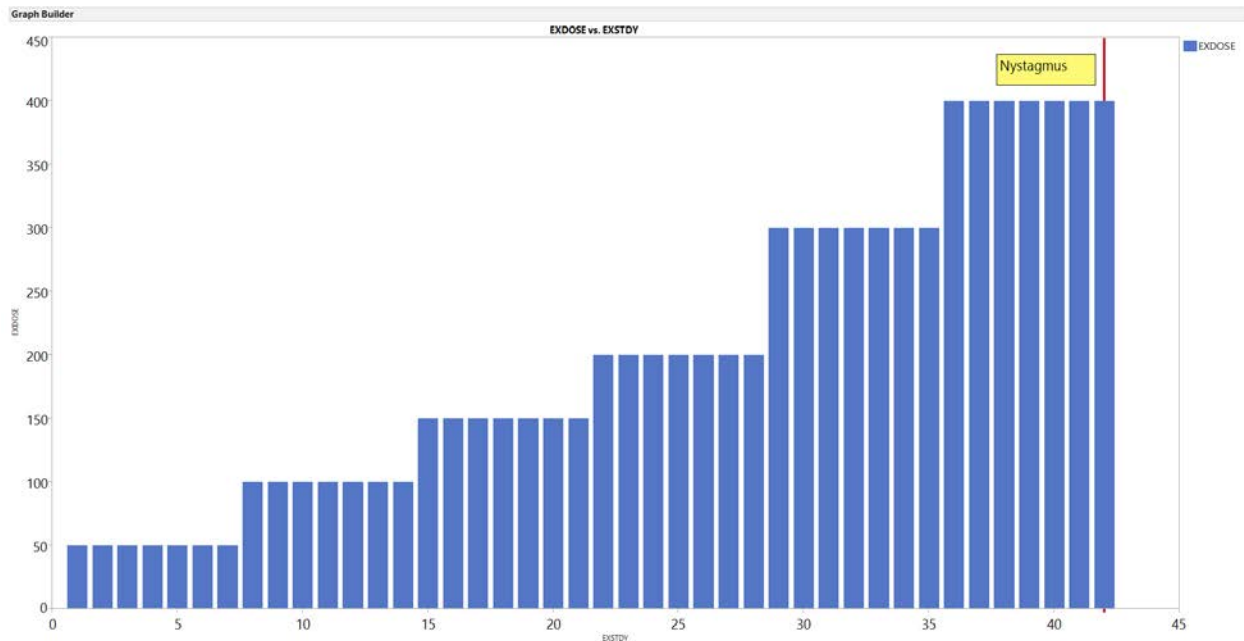


Nystagmus

There were 3 discontinuations due to nystagmus. One patient (YKP3089C017- (b) (6)) is included above under the PT “ataxia”. The remaining case that occurred at a dose of 400mg is presented to examine severity at this dose.

YKP3089C017- (b) (6) (PT nystagmus): 28-year-old Asian male Study Day 42), the subject experienced moderate SAEs of vertigo and nystagmus. As documented in the CIOMS report, the subject was admitted to the hospital on (b) (6). During Visit 5, the subject complained of dizziness, which was assessed as vestibular neuronitis. The subject also had common cold and mild nystagmus. The symptoms aggravated during Visit 6. The subject experienced difficulty in walking and gaze-evoked nystagmus was noted on both eyes. The study drug was withdrawn due to the event of nystagmus and the last dose was taken on study day 42. The symptoms improved with discontinuation of the study drug. *Causal Assessment: The event of nystagmus occurred the 7th day after escalation to 400mg cenobamate daily. There was a preceding event of vertigo. There was a dechallenge response. The temporal relationship to peak dose and dechallenge response support a causal association.*

Figure 33 YKP3089C017- (b) (6) (PT nystagmus), Cenobamate dose by Study Day

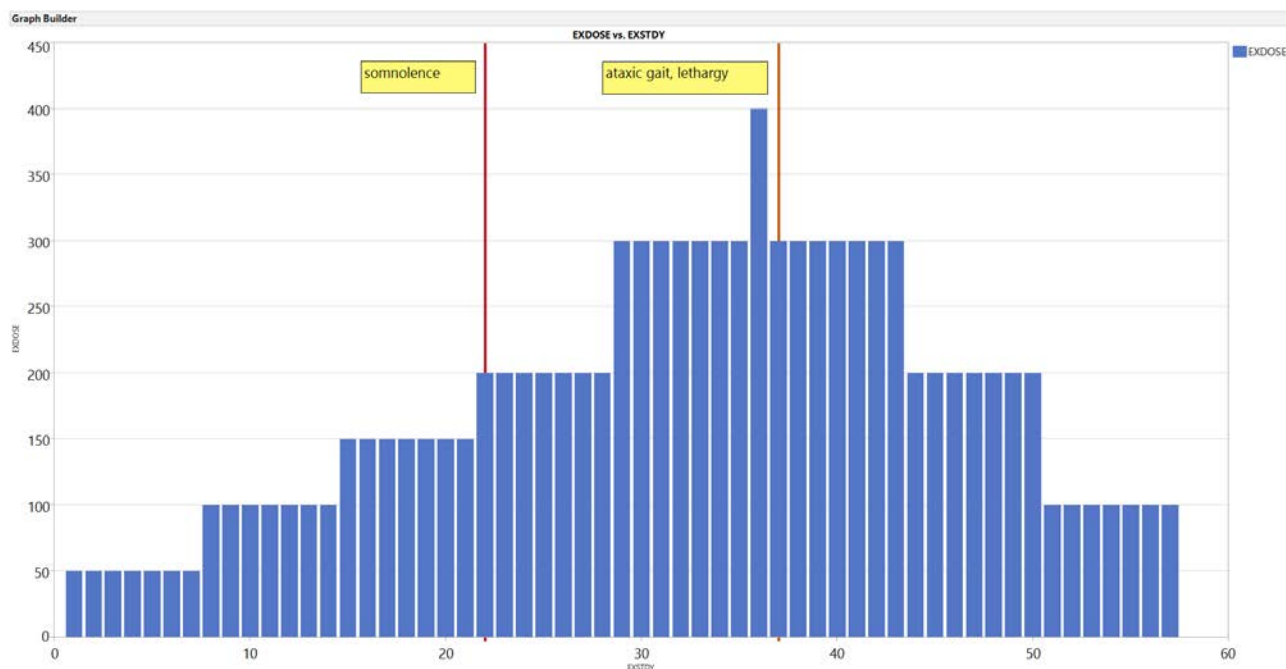


Somnolence

There were 5 discontinuations associated with the preferred term “somnolence” where 4 occurred with cenobamate treatment and one with placebo. A patient who achieved a 400mg dose is chosen for presentation to assess the degree of severity.

YKP3089C017- (b) (6) (PT somnolence): 47-year-old white female Study Day 22), the subject experienced a moderate AE of somnolence. On study day 37 a neurological examination showed the following clinically significant findings: ataxic gait and lethargy see [Figure 34](#). Abnormal laboratory results on the same day are provided in the table below. No treatment was reported for the event. The study drug was withdrawn due to the event and the last dose was taken on study day 56. *Causal assessment: The event of somnolence emerged on day 1 of dose escalation to 200mg of cenobamate while a second preferred term entry for ataxia and fatigue occurred the day following a 400mg dose. There was a dechallenge response entered 1 week after cenobamate discontinuation. The features of the adverse event and timeline of occurrence support a causal relationship.*

Figure 34 YKP3089C017- (b) (6) (PT somnolence), Cenobamate dose by Study Day



Study C021

Analysis of adverse events leading to discontinuation is performed using the 120 day safety update SDTM dataset in JMP Clinical. There were 156 patient discontinuations related to 206 preferred term adverse event entries from the 1344 “enrolled” patient population with positive TEAE flag.

The most frequent SOC’s with greater than 4 adverse events associated with discontinuation were “Nervous system disorders”, “Skin and subcutaneous tissue disorders”, “Psychiatric disorders”, “General disorders and administration site conditions”, “Gastrointestinal disorders”, “Injury, poisoning and procedural complications”, and “Investigations”, see [Table 27](#).

Table 27 Study C021, SOC , Events Associated with Discontinuation

SOC	Event Count	% of Discontinuations
Nervous system disorders	55	26.7
Skin and subcutaneous tissue disorders	47	22.8
Psychiatric disorders	29	14.1
General disorders and administration site conditions	20	9.7
Gastrointestinal disorders	14	6.8
Injury, poisoning and procedural complications	7	3.4
Investigations	5	2.4
Metabolism and nutrition disorders	4	1.9

SOC	Event Count	% of Discontinuations
Infections and infestations	4	1.9
Blood and lymphatic system disorders	4	1.9
Vascular disorders	3	1.5
Respiratory, thoracic and mediastinal disorders	3	1.5
Eye disorders	3	1.5
Cardiac disorders	3	1.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.5
Musculoskeletal and connective tissue disorders	1	0.5
Immune system disorders	1	0.5
Hepatobiliary disorders	1	0.5
Ear and labyrinth disorders	1	0.5

Preferred terms

Frequent Events

The most frequent adverse event preferred term leading to discontinuation was “dizziness” with 14 events from among 14 patients representing 1% of the C021 study population. Twelve of these events occurred in the first 100 days of treatment. Seizure was next in frequency with 9 events from 9 patients. These events occurred between study days 1 and 201 and 66% occurred within the 1st 50 days. Rash followed at the third most frequent event in 9 patients leading to discontinuation. The severity is entered as mild in 6 and moderate in 3 while the 8 had onset before day 47 with one outlier occurrence at day 254. Somnolence followed as the 4th most frequent adverse event leading to discontinuation. There were 8 events from 8 patients. Fatigue followed somnolence as the 5th leading adverse event leading to discontinuation with 8 events from 8 patients. Headache was the 6th leading cause of discontinuation from adverse event with 6 event from 6 patients. All remaining preferred term entries had 5 or less events leading to discontinuation.

Reviewer Comment: From among the most frequent adverse event entries those with preferred terms “dizziness”, “somnolence”, and “fatigue” are seen commonly with antiepileptic drugs, possibly due to CNS depression or neural network dysfunction associated with modification of action potential generation. These events are not unexpected for this drug group.

Seizure: The adverse events due to the preferred term “seizure” are of concern because of the possibility of a proconvulsant effect on some individuals or drug ineffective. Differentiating these possibilities from the occurrence of background seizures in a refractory epilepsy population is difficult. From among these 9 events in 9 patients they were judged as “moderate” in 7 patients, “mild” in one patient and “severe” in one patient. In the case judged as severe, the investigator judged the event as “unrelated” to study drug. All recovered without sequelae. There was no systematic temporal relationship to seizure occurrence with a range from study day 1 to study day 201 with a somewhat even dispersion through this interval. The absence of a temporal relationship weakens the likelihood of a causal relationship.

Rash: Rash was among the most frequent AE preferred terms leading to discontinuation. This was in part, driven by the heightened pharmacovigilance for hypersensitivity reactions included in the design of this study. There were 9 events from 9 patients. Three events were judged by the investigator as moderate in severity and 6 were judged as mild. All are entered as “recovered/resolved”.

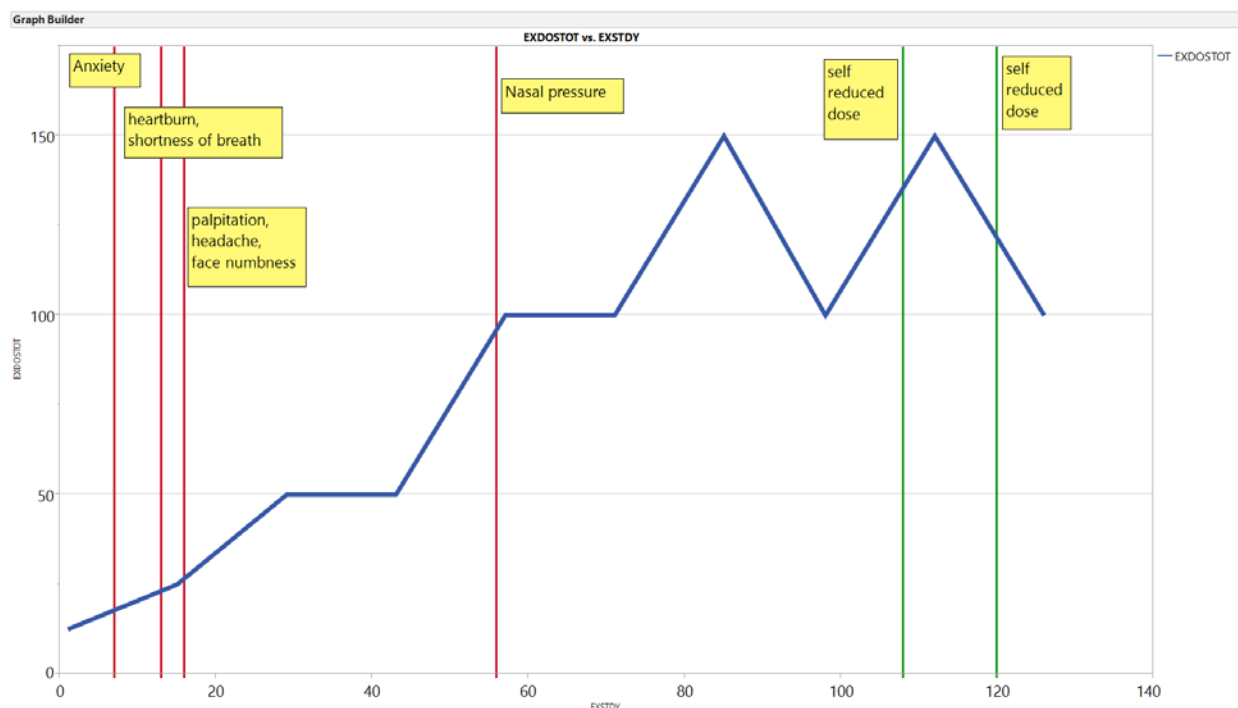
Headache: There were 6 AE’s with the preferred term headache leading to discontinuation. Three events are judged as “moderate” by the investigator, 2 are judged as “mild” and one was judged as “severe” The narrative for the patient (YKP3089C021- (b) (6)) with entry as “severe” was examined. The narrative reveals the patient has a background history of headache. The event began on day 1 of 25mg cenobamate, study day 14. The headache was associated with nausea and vomiting. Cenobamate was discontinued on study day 18 and the patient recovered from headache 14 days after discontinuation. *Causality is probable in this “severe” case due to the temporal relationship to escalation of cenobamate dose.*

Preferred Terms of Interest

The remaining preferred terms are examined for entries of interest due to potential serious, previously unexplored disorders, or due to potential relationship indication of DRESS. These include one presentation each for “dyspnea”, “cardiac failure congestive”, “pyrexia”, “tachypnea”, “thrombocytosis”, “vomiting”, “intentional overdose” and “abdominal pain”.

YKP3089C021- (b) (6) (PT dyspnea): 53-year-old Hispanic male, on study day 7 the subject experienced the mild AE of anxiety, on study day 8 the subject experienced the mild AEs of heartburn and shortness of breath, and on study day 13 the subject experienced the mild AE of blurred vision. On study day 16, while taking 25 mg of study drug, the subject experienced the mild AEs of palpitations of chest, headache, and numbness of face. On study day 56, while taking 50 mg of study drug, the subject experienced the mild AE of nasal pressure. On study day 56 study drug dose was increased to 100 mg, further increased to 200 mg on study day 69. On study day 82, study drug dose was decreased to 150 mg. On study day 94 study drug dose was increased to 200 mg. The subject self-reduced dose to 150 mg on study day 108, and on study day 120 the subject self-reduced dose to 100 mg. The study drug was withdrawn, and the last dose was taken on study day 130. On study day 134, the subject recovered from the events of anxiety, heartburn, shortness of breath, blurred vision, palpitations of chest, headache, numbness of face, and nasal pressure, see Figure 35. *Causal Assessment: This sequence of adverse events may be related to anxiety or uncertain mechanisms of intolerance. The self-reduction of dose beginning at day 108 supports persistent intolerance. The narrative indicates recovery on study day 134 which supports a dechallenge response. There does not appear to be a serious underlying threatening pathophysiology driving this array of symptoms.*

Figure 35 YKP3089C021- (b) (6) (PT dyspnea), Cenobamate Dose by Study Day



YKP3089C021- (b) (6) (PT Cardiac failure congestive): 65-year-old Caucasian male study day 17 the subject experienced the moderate AE of worsening of congestive heart failure, and on study day 23 the subject experienced the mild AE of first-degree AV block. No treatment was reported. The study drug was withdrawn due to the events and the last dose was taken on study day 22. On study day 28, the subject recovered from the event of worsening of congestive heart failure. At the time of study discontinuation on study day 41, the subject was recovering from the event of first-degree AV block. The maximum dose achieved was 25mg daily on study day 16 through discontinuation. *Causal Assessment: The patient has a background history of congestive heart failure. The relationship to worsening of heart failure on the initial dose of 12.5mg is uncertain; however a dose response at this low dose would be unexpected.*

YKP3089C021- (b) (6) (PT Pyrexia): 44-year-old Hispanic male, (study day 1), the subject experienced the mild AE of fever. Specific temperature was not reported. Treatment for the event was not reported. On study day 3, the subject recovered from the event. The study drug was withdrawn due to the event and the last dose was taken on study day 14. The narrative indicates that the patient was started on 12.5mg cenobamate on day 1. The narrative indicates the patient continued cenobamate until day 14, however, the exposure dataset for study C021 does not indicate any drug treatment. *Causal assessment: The relationship of cenobamate to fever is uncertain, in part, because of the divergence between dosing identified in the narrative compared to the exposure dataset. It is possible the patient developed a fever following one dose but there is no associated report of physical or laboratory examination abnormality and no*

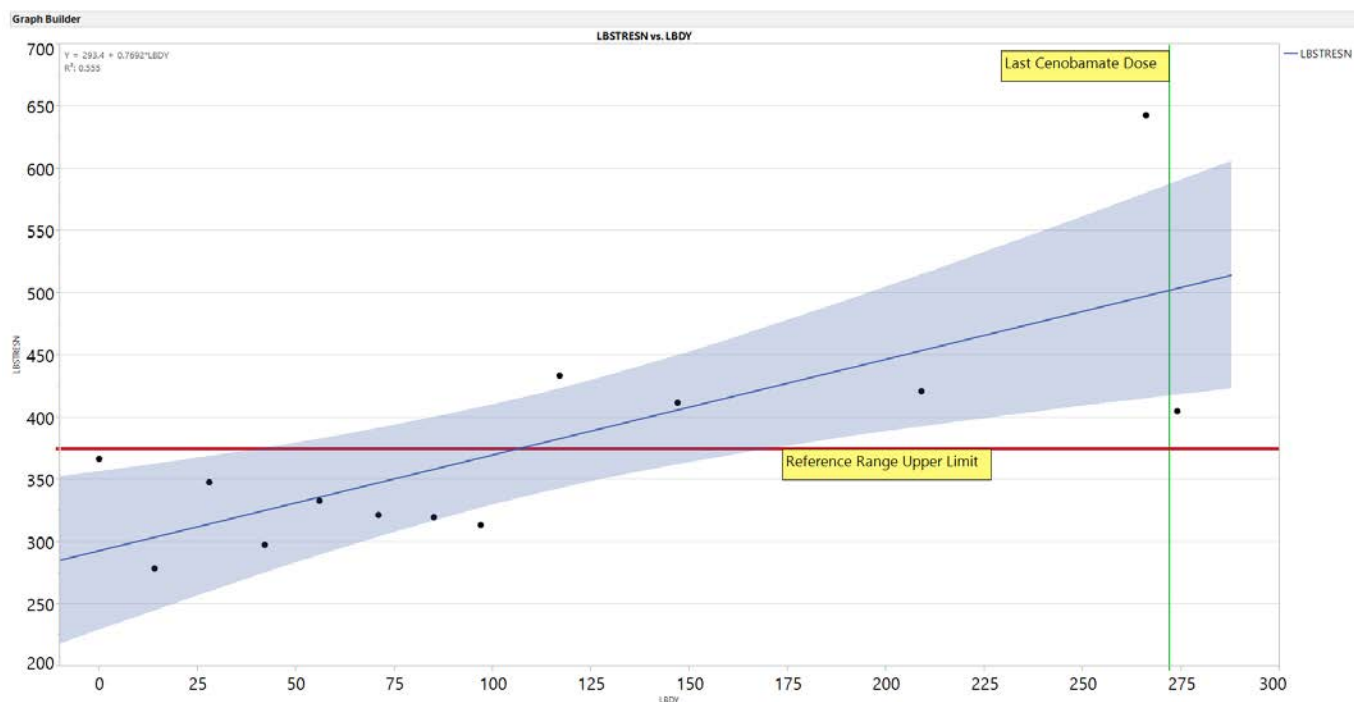
sequala reported.

YKP3089C021- (b) (6) (PT Tachyphrenia): a 50-year-old, Caucasian female. On study day 20, 6 days after transition from 12.5mg to 25mg cenobamate, the subject experienced the mild AE of mind racing, and the moderate AE of anxiety. Treatment for the events was not reported. On the same day the subject recovered from the event of mind racing. On study day 28 while still on 25mg, the study drug was withdrawn. *Causal Association: The patient has a history of “psychosis” related to the introduction of lamotrigine treatment approximately 1 year earlier. The clinical course is uncertain, but the patient was on concomitant lamotrigine 150mg a day at the time of the AE of tachyphrenia. Causality is uncertain, if related, this patient may have a selective vulnerability due to past history of psychosis during lamotrigine treatment.*

YKP3089C021- (b) (6) (PT Abdominal pain): On study day 1 this 27-year-old, Caucasian male experienced the mild AEs of abdominal pain and general malaise. Treatment for the events was not reported. On study day 16 the study drug dose was increased to 25 mg. The study drug was withdrawn due to the events and the last dose was taken on study day 31. *Causal assessment: This event was examined in greater detail due to the identification of 6 entries in study C021 with appendicitis. This event had no further progression beyond abdominal pain. A causal relation to cenobamate is uncertain and this is not a report of appendicitis.*

YKP3089C021- (b) (6) (PT thrombocytosis): 33-year-old Caucasian female study day 273) the subject experienced the severe AE of reactive thrombocytosis. The study drug was withdrawn due to the event and the last dose was taken on study day 272. On study day 308 platelet count was within normal range. Causal Assessment: The patient achieved a dose of 200mg cenobamate on study day 71. Platelet counts averaged over the interval following day 71 was only $12 \times 10^9/L$ greater than baseline if the outlier value of $643 \times 10^9/L$ is removed. This post day 71 average includes the value from termination visit that was 2 days after cenobamate discontinuation. This termination visit value was $238 \times 10^9/L$ lower than the maximum value on study day 266. If cenobamate was the driver of the high platelet count than a decline seen only two days after discontinuation would not be expected due to the long half-life (60hrs) of cenobamate. Overall there appears to be an increase in platelet count related to cenobamate treatment in this patient, but cenobamate is not conclusively related to the high outlier value on study day 266 (see [Figure 36](#)).

Figure 36 YKP3089C021- (b) (6) Platelet Count by Study Day (slope= 0.79, R²=0.56)



Two patients (YKP3089C021- (b) (6), YKP3089C021- (b) (6)) with AE preferred terms of “vomiting” leading to discontinuation were examined. These events were judged mild and moderate by the investigator. Examination of the narrative report does not reveal a threatening level of severity.

Two patients (YKP3089C021- (b) (6), YKP3089C021- (b) (6)), with a preferred term entry of “intentional overdose” are examined further to determine if an AE of “suicide attempt” was also present in the adverse event dataset. In both cases the “intentional overdose” was also captured as a suicide attempt.

Reviewer Comment: Discontinuations in study C021 provide insight into potentially significant adverse event among a large sample of cenobamate treated patients with the reduced dose escalation schedule. The most frequent adverse events are common for Antiepilepsy drugs. These include those associated with altered neurotransmission such as “somnolence”, “dizziness”, and “ataxia”. There is no unexpected safety signal in the frequency of these events, and they are considered in labeling. The frequency of “seizure” and “epilepsy” do not give rise to a signal for ineffective drug or a pro-convulsant effect. The frequency of “headache” and “nausea” indicate potential for difficulty with tolerability in a proportion of patients but do not rise to the level of a serious physiologic threat or broad difficulty with tolerance. Discontinuations in the “Psychiatric disorders” SOC including preferred terms “irritability”, “anxiety”, “suicidal ideation” and “suicide attempt” reveal that cenobamate has some adverse

psychoactive quality. The frequency of discontinuation due to these “psychiatric disorder” SOC adverse events is 1%. The subset of suicide related terms is 0.4%. The frequency of discontinuations due to suicidality terms does not appear out of alignment with current Antiepilepsy drug class labeling for “Suicidal Behavior and Ideation” in Section 5.

Seven selected preferred terms were examined to assess the level of threat represented by the adverse event. Three of the select preferred term events, “dyspnea”, “abdominal pain” and “vomiting” are present in the package insert, adverse reactions table. The remaining 4 terms “cardiac failure”, “tachyphrenia”, “thrombocytosis”, and “intention overdose” do not reach a level of evidence to support a new cenobamate specific safety signal.

8.4.5. Significant Adverse Events

Appendicitis

The average exposure per patient in the ISS 120-day safety exposure dataset is 1.578 years per patient. This was the average exposure for 1945 patients who received cenobamate in the pivotal studies and their open label extensions and study C021. This estimate yields 3070 patient years of total exposure. There were 9 cases of appendicitis identified in the same safety dataset, see [Table 28](#). This yields a frequency of 2.9 cases of appendicitis / 1000 patient years of exposure. This is greater than the reported background incidence of 1.1/1000 population per year based on the literature-based appendicitis risk assessment below.

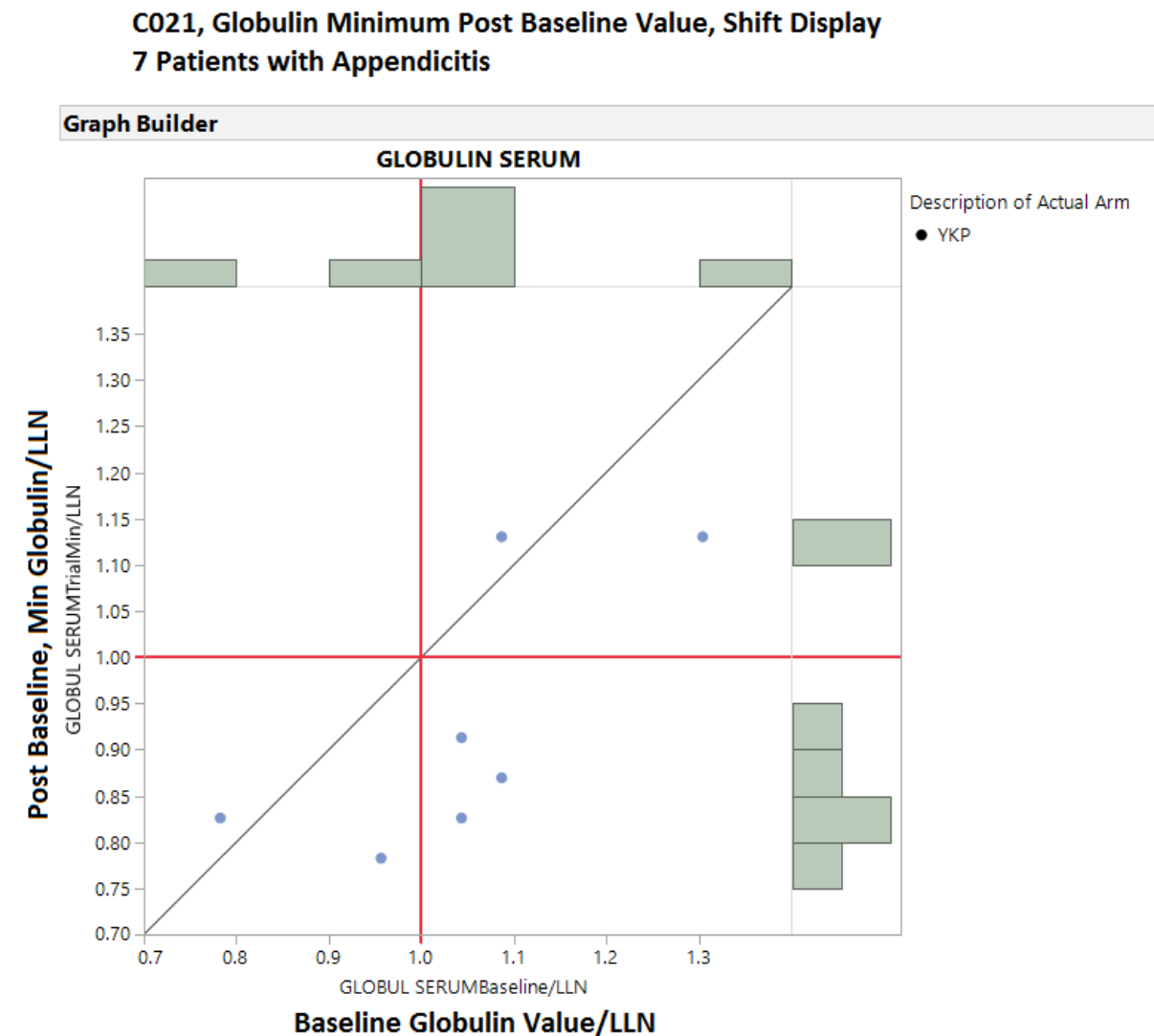
The mean and median age of patients that experienced appendicitis was 35.5 and 36 years respectively with a range of 26 to 44 years. Sixty six percent of patients were male while 33 percent were female, all but one was Caucasian. This age distribution is similar to the distribution of the cenobamate treatment population as a whole where the mean and median ages were 39.5 and 38 respectively. The racial distribution is also in alignment with the cenobamate treatment population where 78.5 percent were Caucasian. There is a predominance of males in the appendicitis group compared to the distribution of the cenobamate treatment population where 49.7 percent of patients were female.

Table 28 All Studies, 9 Cases of Appendicitis

STUDY ID	USUBJID	Preferred Term	DOSE	AESDY	SEX	AGE	RACE
C021	YKP3089C021- (b) (6)	APPENDICITIS	300	221	M	33	WHITE
C021	YKP3089C021- (b) (6)	APPENDICITIS	400	232	M	43	WHITE
C021	YKP3089C021- (b) (6)	ACUTE APPENDICITIS	300	259	M	35	WHITE
C021	YKP3089C021- (b) (6)	APPENDICITIS	100	264	F	26	WHITE
C021	YKP3089C021- (b) (6)	COMPLICATED ACUTE APPENDICITIS	350	349	M	44	OTHER
C021	YKP3089C021- (b) (6)	APPENDICITIS	200	395	F	36	WHITE
C021	YKP3089C021- (b) (6)	ABDOMINAL PAIN	200	438	F	27	WHITE
C017	YKP3089C017- (b) (6)	APPENDICITIS PERFORATED	200	592	M	39	WHITE
C017	YKP3089C017- (b) (6)	APPENDICITIS	300	1267	M	37	WHITE

YKP3089C021- (b) (6) (PT Abdominal Pain): 29-year-old Caucasian female the patient experienced the severe serious adverse event of abdominal pain on study day 438, presented to the Emergency Department (ED) and was admitted. (Since study day 190, the patient had a mild AE of gallstones, which remained ongoing). On study day 441 the subject underwent an appendectomy and cholecystectomy. Treatment while hospitalized included post-operative pain management with oxycodone 5 mg oral three times a day, and paracetamol 1000 mg oral three times a day, ongoing since study day 442. The site confirmed the discharge summary was unobtainable. The study drug was not changed due to the event, although the last entry for cenobamate treatment in the exposure dataset is day 444.

Figure 37 Globulin Minimum Value Post Baseline for Study C021 Patients with Appendicitis



LITERATURE RISK ASSESSMENT

Lifetime risk 6-9%¹¹ overall incidence of appendicitis in the United States, 1.1 per 1,000 population per year¹²

Reviewer Comment: The analysis of appendicitis frequency reveals a signal for an increase over the background population rate. A concurrent analysis of serum globulin ([Figure 37](#)) reveals a trend of decline in globulin five of seven patients in study C021 that developed appendicitis. There is no clearly vulnerable subpopulation. Identification of this signal in [labeling is recommended](#), see Section 10.1, Prescription Drug Labeling.

Hyponatremia

Controlled study data reveals a dose related frequency of sodium values in the laboratory dataset with separation from placebo. All instances are confounded by concomitant oxcarbazepine or carbamazepine. However, there is separation from placebo, yet the background confounding medications are constant across placebo and treatment. The observed separation from placebo is supportive of an independent effect of cenobamate on sodium values but is not sufficiently clear to enter into labeling.

Hyperkalemia

There was a signal for post baseline elevation of potassium identified in both studies C013 and C017. There was notable excess of high post baseline potassium values with cenobamate treatment. In study C017 there was an excess of high outlier potassium values in the cenobamate treatment arm over the placebo arm. There was also a higher frequency of post baseline shift from normal to OORR high in the cenobamate arm. In study C017 there was an excess of high baseline potassium values in study C017, however, the post baseline distribution of OORR high values was dose related with an increasing frequency of high values as cenobamate dose increased. The laboratory abnormalities subsection of section 6 should reflect that OORR high potassium values were in excess of placebo in a dose related distribution, occurring in 5.6%, 8.3%, 9.1% and 10.8% of the placebo, 100mg, 200mg, and 400mg treatment arms respectively, with a maximum value of 5.9meq/L.

¹¹ 2. Flum DR, Koepsell TD. Evaluating diagnostic accuracy in appendicitis using administrative data. Journal of Surgical Research 2005;**123**(2):257-61 doi: 10.1016/j.jss.2004.08.020[published Online First: Epub Date]].

¹² 1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. THE EPIDEMIOLOGY OF APPENDICITIS AND APPENDECTOMY IN THE UNITED-STATES. American Journal of Epidemiology 1990;**132**(5):910-25 doi: 10.1093/oxfordjournals.aje.a115734[published Online First: Epub Date]].

Headache

The ISS 120-day ADAE dataset where all AESDY (*start date relative to 1st dose date*) entries are positive, was examined. This revealed that 297 patients had 509 entries for the preferred term headache.

One headache adverse event entry (YKP3089C021-^{(b) (6)}), on treatment day 72 was an SAE. The narrative report reveals the patient had a past history of headache pre-dating cenobamate treatment by 5 years. The headache event on treatment day 72 was associated with nausea, vomiting, and chest pain. The narrative indicates “cardiac work-up including echocardiogram, all negative”. Cenobamate was discontinued on study day 71. The headache was treated with Fiorinal one tablet PO four times a day for 4 days. On study day 78 the patient experienced a moderate SAE of multiple seizures and was hospitalized. This may represent withdrawal seizure (although the long half-life of cenobamate should allow a physiologic taper).

From among the remaining 508 headache events there were 356 (70%) judged by the investigator as “mild” severity, 142 (28%) were judged as “moderate” severity and 10 were judged as “severe”. The mean and median time to headache AE from start of cenobamate were 330 day and 140 days respectively. Approximately 65% of headache AE occurred by treatment day 270, see [Figure 38](#).

Figure 38 C021 Kaplan–Meier Plot of 508 Headache TEAE Entries by Study Day and Proportion of Events.

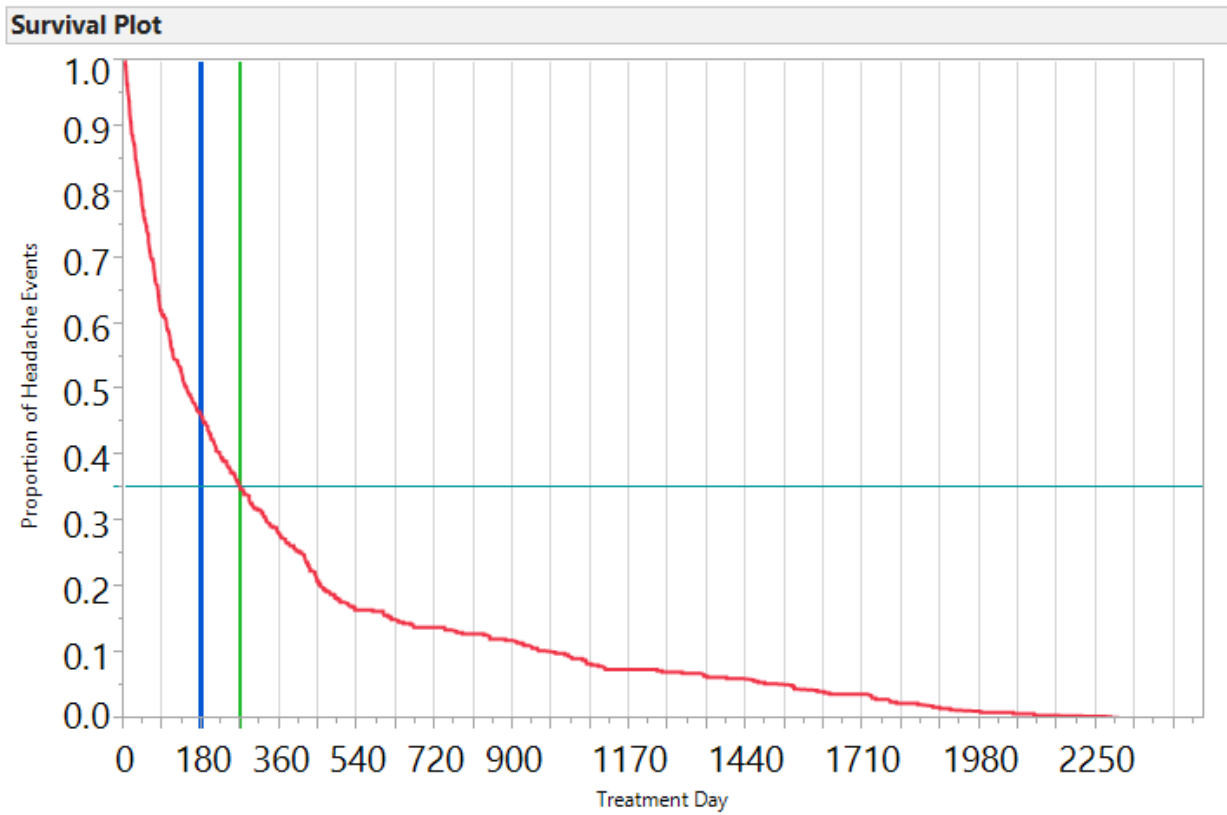


Table 29 Headache, All Cenobamate Withdrawals, C013- C017 DB - OLE, C021

USUBJID	AESDY	Treatment days	Dose (mg)	Severity	AGE	SEX	Race	Ethnic	Treatment	Outcome	Clinical
YKP3089C021-(b) (6)	2	3	12.5	Moderate	55	F	caucasian	not Hispanic or latino	none	resolved	none
YKP3089C021-(b) (6)	14	17	25	Severe	47	M	African-American	not Hispanic or latino		resolved	nausea, vomiting, severe headache
YKP3089C021-(b) (6)	16	136	25	Mild	53	M	other	Hispanic or latino			palpitations of chest, headache, and numbness of face
YKP3089C021-(b) (6)	19	14	12.5	Mild	36	F	other	Hispanic or latino	acetaminophen	resolved	past history of headache
YKP3089C021-(b) (6)	25	28	25	Moderate	35	F	African-American	not Hispanic or latino	ibuprofen	resolved	
YKP3089C021-(b) (6)	133	285	100	Mild	35		caucasian	Hispanic or latino	metaprolol and sumatriptan	resolved	
YKP3089C021-(b) (6)	221	303	200	Moderate	32	F	Other	Hispanic or latino	dose reduction,	Resolving	noted to be recovering, several stages of dose reduction performed but noted to be recovering 83 days after AE and 22 days after discontinuation
YKP3089C013-(b) (6)	273	348	200	Moderate	49	M	Asian	not Hispanic or latino	not reported	not recovered	PMH , intermittent headache
YKP3089C017-(b) (6)	634	643	200	Moderate	30	F	other	Hispanic or latino	imitrex	not reported or not resolved	

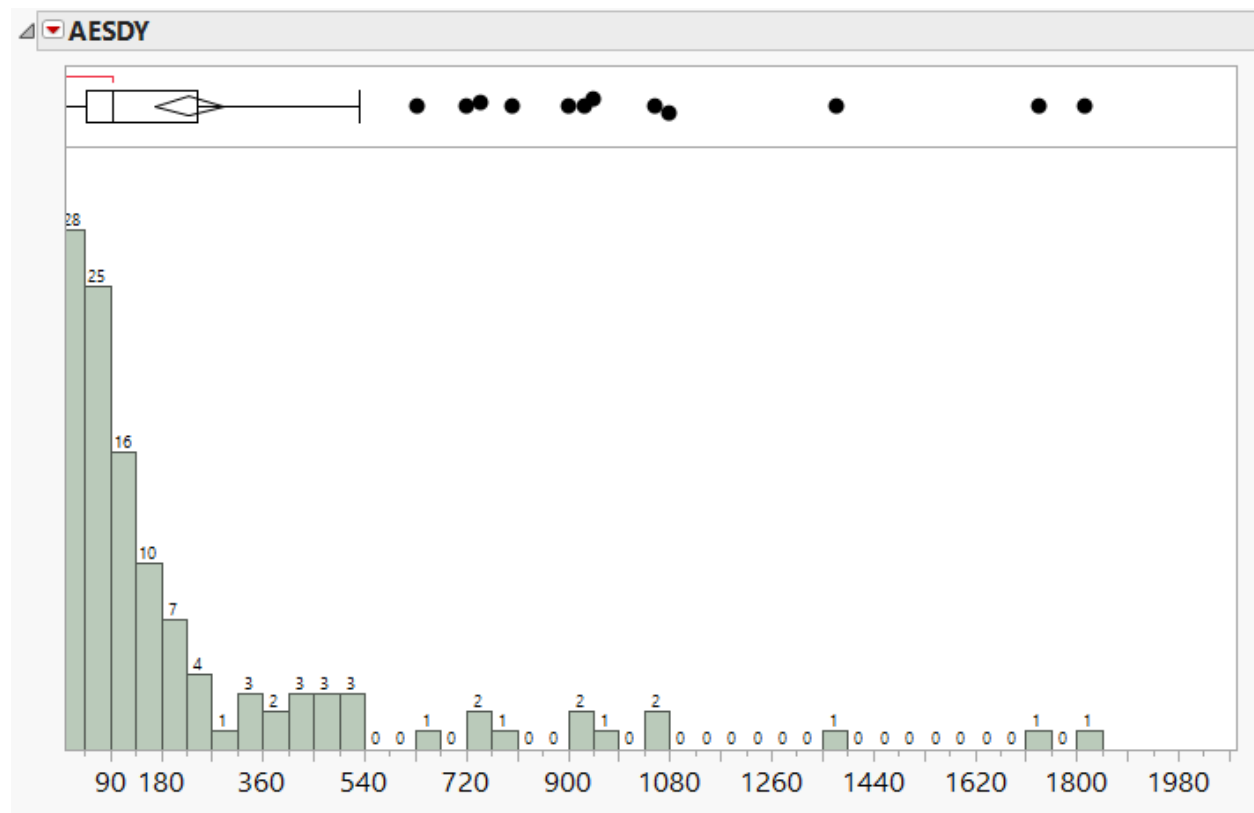
Reviewer Comment: The adverse event of headache is frequent with an occurrence in 15% of cenobamate treated patients. Sixty-five percent (65%) of occurrences were in the first 9 months of cenobamate treatment. Seventy percent are judged as “mild”

severity by investigators and 2% judged as “severe”. There were 9 (0.46%) withdrawals due to headache or associated with headache. In two reports there was a prior history of headache. There is a signal for frequent headache, however the events appear to abate with adaptation to cenobamate treatment and most are self-limited.

Constipation

There were 116 non-serious TEAE events of “constipation” from 102 (5.2%) patients where 89 (76% of all constipation) events from 82 patient occurred within the first 250 days of cenobamate treatment and 39 (35% of all constipation) events occurred within the first 60 days of treatment, see Figure 39. Ninety events (78% of constipation) were judged by the investigators as mild, 24 were judged by investigators as moderate and 2 were judged as severe.

Figure 39 Studies C013, C017, and C021 DB & OL, Constipation Events by Study Day



A notable event of obstipation possibly resulting from constipation occurred in study C021. There was one SAE of constipation on study day 18 in study C021 (YKP3089C021-^{(b) (6)}). A 44-year-old Caucasian male patient experienced the moderate SAE of obstipation and was hospitalized. The patient presented to the emergency medical service due to abdominal pain in epigastrium with propagation into the lumbar region on the left. The patient

had no vomiting, no dysuria, no fever, and had a bowel movement that day. An ultrasound revealed an obstructed pancreas. During hospitalization the patient received analgesic and spasmolytic therapy, diet, and enema. During the enema he evacuated a large amount of stool. The study drug was not changed due to the event. On study day 20, the patient recovered from the event of obstipation and was discharged from the hospital in good condition. Concomitant medications included: Vigantol 2 gtt oral one a day for prevention of osteoporosis, ongoing since (b) (6) and acidum folicum 10 mg oral once a week for mild thrombocytopenia, ongoing since (b) (6). Concomitant AEDs included: clobazam 25 mg oral daily, from (b) (6) - (b) (6) to (b) (6), valproate chrono 1000 mg oral twice a day, from (b) (6) to (b) (6), Lamictal 1000 mg oral twice a day, ongoing since (b) (6).

Reviewer Comment:

Gastrointestinal disorders were evaluated as to determine if there were events related to constipation. The occurrence of abdominal pain was of potential concern. The co-investigation of “Gastrointestinal disorders” with “constipation” did not reveal any unifying process or family of related adverse events. Constipation was common and there was a single SAE of “obstipation” which was likely related to constipation because it was relieved by an enema. Proposed labeling covers this event in section 6, adverse reaction table.

Psychiatric

One percent of patients treated with cenobamate in the ISS dataset had an SAE in the group including the following terms. High impact terms representing a safety threat are selected from all “psychiatric disorder” SOC terms in the ISS on treatment safety dataset. The terms identified to represent this category were “suicide attempt”, “suicidal ideation”, “psychotic disorder”, “aggression”, “completed suicide”, “anxiety”, “anxiety disorder”, “depression”, and “major depression”, [Table 30](#). One percent of patients experience these events.

Table 30 ISS- SOC, SAE, High Safety Threat “Psychiatric Disorders” Preferred Terms with Frequency (n=1945)

AEDECOD	# Patients	% Patients (n=1945)
Suicide attempt	5	0.26
Suicidal ideation	4	0.21
Psychotic disorder	3	0.15
Aggression	2	0.1
Completed suicide	2	0.1
Anxiety	1	0.05
Anxiety disorder	1	0.05
Depression	1	0.05
Major depression	1	0.05
Total	20	1.0

To assess causality the temporal relationship between treatment and event onset was assessed. Events are more likely to be causal with a close temporal relationship. Due to the potential long latency needed to influence the complex central nervous system output of psychiatric disorders, an estimate of 1 year is selected as containing events with the most plausibly causal relationship to cenobamate treatment. This analysis reveals that approximately 14 of 21 events (66%) fell within the one-year timeframe, [Table 31](#).

Table 31 ISS-SOC, SAE, High Safety Threat “Psychiatric Disorders” Preferred Terms by Treatment Day of Occurrence.

Patient ID	Preferred Term	Study Day on Treatment
YKP3089C013- (b) (6)	Completed suicide	132
YKP3089C013- (b) (6)	Aggression	441
YKP3089C017- (b) (6)	Suicidal ideation	93
YKP3089C017- (b) (6)	Suicide attempt	69
YKP3089C017- (b) (6)	Completed suicide	1499
YKP3089C017- (b) (6)	Suicidal ideation	77
YKP3089C017- (b) (6)	Psychotic disorder	727
YKP3089C017- (b) (6)	Psychotic disorder	1310
YKP3089C021- (b) (6)	Anxiety disorder	50
YKP3089C021- (b) (6)	Suicidal ideation	441
YKP3089C021- (b) (6)	Suicidal ideation	407
YKP3089C021- (b) (6)	Anxiety	414
YKP3089C021- (b) (6)	Psychotic disorder	18
YKP3089C021- (b) (6)	Suicide attempt	144
YKP3089C021- (b) (6)	Depression	146
YKP3089C021- (b) (6)	Suicide attempt	188
YKP3089C021- (b) (6)	Suicide attempt	173
YKP3089C021- (b) (6)	Psychotic disorder	102
YKP3089C021- (b) (6)	Suicide attempt	190
YKP3089C021- (b) (6)	Aggression	144
YKP3089C021- (b) (6)	Major depression	22

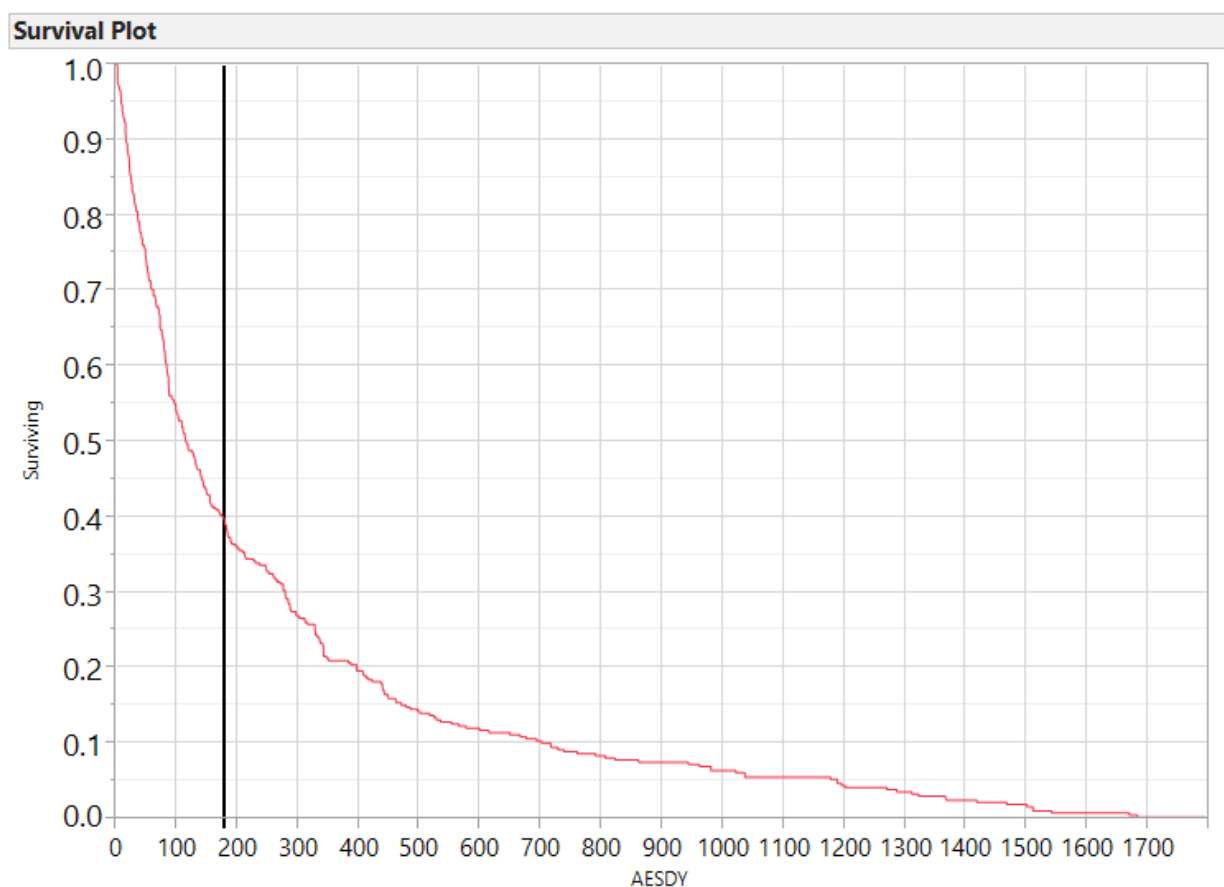
There were two completed suicide events in the safety dataset. One occurred at study day 132 and the second at day 1499 (4.1 years) of treatment. The 1st case (YKP3089C013- (b) (6)) has a plausible causal relationship to cenobamate treatment. A causal relationship is remote due to the prolonged interval between the adverse event and start of cenobamate. This long interval allows the potential for multiple intervening variables to influence the psychiatric status of the patient. There was also a suicide attempt on day 183. This event has a plausible temporal relationship to cenobamate treatment.

Table 32 Complete Suicide – Near Complete Events

USUBJID	SUBJID	day	PT	Clinical event	comment
YKP3089C013-	(b) (6)	132	completed suicide	multiple stab wounds	
YKP3089C021-	(b) (6)	183	suicide attempt	multiple stab wounds	
YKP3089C017-	(b) (6)	1499	completed suicide	Hanging	

The overall frequency in the ISS safety dataset (n=1945) for the SOC “psychiatric disorders” is examined. There were 358 events in this SOC from 272 (14%) patients. A causal relationship to cenobamate treatment is supported by a close temporal relationship. The decay curve of total events over time is shown in Figure 40. This analysis reveals that approximately 60 percent of the “Psychiatric disorders” adverse events occurred in the 1st six months. These are more likely to be causally related, leaving the remaining 40% as less likely related.

Figure 40 ISS, SOC “psychiatric disorders” Kaplan–Meier Plot of the Proportion of Adverse Event Occurrence by Study Day (day 0 – 1700)



Events that capture “Suicidal Behavior and Ideation” are examined in the ISS dataset. The preferred terms “completed suicide”, “intentional self-injury”, “suicidal ideation”, and “suicide attempt” capture 39 events from 36 (1.9%) patients. Approximately 50% of these events occur

in the first 6 months and 80% in the first year after beginning cenobamate treatment. The longer the latency to an event the less likely the causal association.

Suicidality terms are examined in the double-blind studies. In study C017 there were 2 suicidality terms, “suicidal ideation” and “suicide attempt”. Three terms from 3 patients (1.8%) appeared in the 100mg treatment arm and 1 term (0.9%) in the 200mg treatment arm with none in placebo. In study C013 the same terms are examined. there was one entry each for “suicidal ideation” in the placebo and cenobamate (200mg) treatment arm yielding a frequency of 0.92% and 0.9% respectively.

The more threatening adverse events that are captured by the preferred terms “aggression”, “agitation”, “anger” and “hostility” are examined for frequency and temporal relationship to the start of cenobamate treatment. There were 36 entries for these terms from 35 (1.8%) patients. Approximately 70% of the events occurred in the 1st six months. These events are more likely to be causally related to treatment. There was one entry for the preferred term “homicidal ideation”. This event occurred at day 1020 (2.8 years). This long latency reduces the likely causal relationship.

The adverse events related to psychosis are captured by the preferred terms “delusion”, “hallucinations”, “hallucination, auditory”, “hallucination, visual”, “Paranoia”, “persecutory delusion”, “Psychotic disorder”, and “thinking abnormal”. There were 28 entries from this preferred term grouping from 18 (0.9%) patients. Approximately 45% of these events occurred in the first six months of cenobamate treatment leaving 65% with a latency greater than 6 months. This latter group has a less likely causal relationship to treatment.

Reviewer Comment, Psychiatric Disorders

Examination of the adverse event preferred terms, frequency and temporal distribution across the ISS dataset reveals a suicidality is plausibly related to study drug but does not appear to be out of alignment with the risk identified in current AED class labeling in section 5 for “*Suicidal Behavior and Ideation*”. There is a possible signal for an association between cenobamate treatment and the psychiatric disorder terms aggression, agitation, anger, and hostility. This signal is confounded by the severity of underlying illness as well as potential confounding medications. When a temporal relationship of 6 months is considered supportive the frequency of these events is 1.3%. This frequency does not reach a substantive threshold for additional labeling. The terms for psychosis are less substantive in causal relationship due to low frequency, underlying illness and a temporal relationship that is not tightly coupled in 55% of events.

Cardiac Adverse Events

Conduction Abnormalities

YKP3089C021- (b) (6) (PT Atrioventricular block complete) also discussed in [section 8.4.2 “Serious Adverse Events” Study C021](#). All Adverse events during the study

Table 33 Study C021, Patient YKP3089C021- (b) (6) All TEAE and SAE by Study Day, Severity, Action Taken.

AEDECOD	AESEV	AESER	AEACN	AEREL	AESDTH	AESHOSP	AE SLIFE	AESTDY
Fatigue	MILD	N	DOSE NOT CHANGED	REMOTE				48
Dermatitis contact	MILD	N	DOSE NOT CHANGED	REMOTE				48
Ligament sprain	MILD	N	DOSE NOT CHANGED	UNRELATED				94
Seizure	MODERATE	N	DOSE INCREASED	UNRELATED				127
Nausea	MILD	N	DOSE NOT CHANGED	UNRELATED				127
Urinary tract infection	MILD	N	DOSE NOT CHANGED	UNRELATED				127
Atrioventricular block complete	SEVERE	Y	DOSE NOT CHANGED	UNRELATED			Y	185
Deep vein thrombosis	MODERATE	Y	DOSE NOT CHANGED	UNRELATED		Y		185
Vomiting	MILD	N	DOSE NOT CHANGED	UNRELATED				325

Table 34 Study C021, Patient YKP3089C021- (b) (6) Exposure by Study Day

YKP3089C021- (b) (6)	EXDSTOT	EXSTDY	EXENDY
	12.5	1	14
	25	15	28
	100	29	41
	100	42	55
	100	56	69
	150	70	83
	200	84	98
	200	99	111
	200	112	131
	250	132	141
	250	142	199
	250	200	258
	250	259	358
	250	359	448

Death, SAE, TEAE Examination of ISS

Death-

58 yo cardiac arrest Chest Pain, diaphoresis, collapse after 1.9years of treatment C013 OL

MI, 60 female, Event after 3.1 years of treatment on lacosamide, sudden abdominal pain, collapse, unresponsive, prior “cardiovascular accident.

Table 35 ISS Deaths Under SOC “Cardiac Disorders”

Patient ID	Preferred term	SAE	Study Day

YKP3089C013-	(b) (6)	Cardiac arrest	Y	697
YKP3089C017-	(b) (6)	Cardiogenic shock	Y	841
YKP3089C017-	(b) (6)	Myocardial infarction	Y	1143

SAE

POOL DB:

no cardiac disorders events

PIVOTAL OLE – C021

Table 36 ISS SAE Under SOC “Cardiac Disorders”

USUBJID	AEDECOD	SAE	Study day	Additional information
YKP3089C021- (b) (6)	Acute myocardial infarction	Y	170	
YKP3089C021- (b) (6)	Atrioventricular block complete	Y	185	
YKP3089C013- (b) (6)	Sinus node dysfunction	Y	224	
YKP3089C013- (b) (6)	Angina pectoris	Y	427	
YKP3089C017- (b) (6)	Bundle branch block left	Y	562	
YKP3089C017- (b) (6)	Pericarditis	Y	580	
YKP3089C013- (b) (6)	Cardiac arrest	Y	697	58 YO
YKP3089C017- (b) (6)	Cardiogenic shock	Y	841	39 yo unexplained 2.3 yr treatment, underlying dyslipidemia, SUDEP is possible
YKP3089C017- (b) (6)	Myocardial infarction	Y	1115	
YKP3089C017- (b) (6)	Cardiac arrest	Y	1142	ictal arrest
YKP3089C017- (b) (6)	Myocardial infarction	Y	1143	60 yo

TEAE

DB POOL:

Events that were not rate related, tachycardia, bradycardia are considered. One patient in the 200mg treatment arm had an entry for PT “atrial flutter” on day 1 and day 86.

PIVOTAL OLE – C021:

Excluding SAE’s there were 34 Events from 29 (1.5%) patients. There were 4 patients with anginal symptoms, one with no study day, two within 3 months and one at 3.3 years. One patient developed atrial fibrillation – flutter on day 224 and another patient has two entries for atrial fibrillation, on days 357 and 453 respectively. Five patients have entries for 1st degree block, one on day 23 the remaining 4 between day 152 and 491. A 65-year-old patient has an entry for “Cardiac failure congestive” on day 17 and cenobamate was withdrawn. This patient has a past history of CHF in the medical history dataset. One patient has an entry for “coronary artery disease” on day 1126.

Clinical Review
Steven Dinsmore, DO
NDA 212839 (cenobamate) XCOPRI

A 21-year-old patient has an entry for left atrial enlargement on day 358 with no past medical history of heart disease. One 36 yo female has an entry for “myocardial ischemia” on day 363, there is no history of heart disease. There is an entry for “pulmonary hypertension” on day 391 – follow up. The myocardial ischemia is entered as “mild” severity and cenobamate is continued. A 47 yo male patient has an entry for “myocardial infarction” on day 1115 (3 years). Cenobamate is continued and the event is identified as “moderate” severity. The remaining preferred term entries are for three patients with palpitations, these all occur within the first 69 days. One occurred on day 16 and cenobamate was withdrawn approximately day 146 for non-cardiac cause. The remaining cardiac TEAE entries were entries under the terms “tachycardia”, “bradycardia”, “sinus bradycardia” and “sinus node dysfunction”. None had study drug withdrawal. The “sinus node dysfunction is identified as “severe” intensity. This occurred on day 229.

Syncope:

there were 16 syncope events from 10 patients entered in the Phase 2 ISS.

Table 37 ISS, Syncope Phase 2/3 Studies

USUBJID	AETERM	AEDECOD	AESER	AEACN	AEOUT	ASEV	AESDY
YKP3089C021- (b) (6)	VASOVAGAL SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Moderate	9
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	38
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	53
YKP3089C013- (b) (6)	PATIENT FAINTED FOR A FEW SECONDS (AFTER BLOOD DRAW)	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	85
YKP3089C021- (b) (6)	FAINTED	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	92
YKP3089C021- (b) (6)	VASOVAGAL SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	106
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	109
YKP3089C021- (b) (6)	FAINTING/PHONE INFORMATION FROM PATIENT/	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Moderate	303
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	316
YKP3089C013- (b) (6)	SYNCOPE EPISODES (INTERMITTENT)	Syncope	N	DOSE NOT CHANGED	NOT RECOVERED/NOT RESOLVED	Moderate	320
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	321
YKP3089C017- (b) (6)	MICTURITION SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Moderate	323
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	325
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	338
YKP3089C021- (b) (6)	SYNCOPE	Syncope	N	DOSE REDUCED	RECOVERED/RESOLVED	Mild	340
YKP3089C013- (b) (6)	FAINTING SPELL	Syncope	N	DOSE NOT CHANGED	RECOVERED/RESOLVED	Mild	542

Reviewer Comment, Cardiac Disorders

The fatal outcome events of “cardiac arrest”, “cardiogenic shock” and “myocardial infarction” did not have a temporal relationship to initiation of cenobamate that supports causality. One patient had a background cardiac risk history, a second may have been SUDEP. The third case with the shortest latency from cenobamate start of 1.9 years had no clear cause. Examination of syncope revealed sporadic events was performed across an exposure period from day 9 to 542 involving 0.6% of patients. None of the syncope were entered as an SAE and none had cenobamate discontinued. The remaining analysis of events did not identify a trend of threatening cardiac events with compelling temporal relationship or frequency that identifies a specific cardiac safety signal.

Hepatic Transaminases, Hy’s Law

Examination of study C013 revealed no post baseline ALT or AST values >3 x ULN. In patients with normal baseline the distribution of OORR high values for ALT and AST both reveal that 7 (6.4%) patients in the placebo arm and 9 (8%) patients in the cenobamate (200mg) arm had at least one post baseline OORR high value. In study C017, from among patients with a normal baseline value, there were 1 (0.9%), 1 (0.9%), 4 (3.6%), and 8 (7.1%) patients with an elevation of post baseline ALT to a value OORR high. There was 1 (0.9%) patient in the 100mg treatment arm, 2 (1.8%) patients in the 200mg treatment arm, and 3 (2.7%) patients in the 400mg treatment arm and none in placebo, with a post baseline elevation to > 3 x ULN. There was a maximum elevation in patient YKP3089C017- (b) (6) to 7.6 x ULN at visit 6 (day 43), there was no concurrent elevation in bilirubin. study drug was discontinued on study day 48 with a decline to 4.2 x ULN at study day 127 and 2.1 x ULN at study day 162. There were no Hy’s law cases.

There were 308 (23.4%) patients with a post baseline maximum value for ALT during the course of the study that were OORR high and were an increase from the baseline value. These 308 values occurred from among 12036 post baseline measurements across study visits 3 to 14 and represent 2.6% of measurements. There were 42 instances from 32 (1.6%) patients with ALT > 3 x ULN. The extreme outliers are examined. A trend of sustained and sequential elevation of ALT values is generally not present. There were no Hy’s law cases in the C021 laboratory dataset and no signal for sustained and sequential escalation of ALT.

Visual Acuity Disturbance

Table 38 Vision Disorder Adverse Events, C013, C017 DB Interval

PT	Treatment	# Patients	# in Treatment Group	% in Dose Group
BLINDNESS UNILATERAL	200mg	1	223	0.4
DIPLOPIA	100mg	8	108	7.4
DIPLOPIA	200mg	15	223	6.7
DIPLOPIA	400mg	17	111	15.3

PT	Treatment	# Patients	# in Treatment Group	% in Dose Group
DIPLOPIA	Placebo	4	216	1.9
VISION BLURRED	100mg	2	108	1.9
VISION BLURRED	200mg	5	223	2.2
VISION BLURRED	400mg	4	111	3.6
VISION BLURRED	Placebo	1	216	0.5
VISUAL IMPAIRMENT	200mg	2	223	0.9
VISUAL IMPAIRMENT	400mg	1	111	0.9

C021 TEAE

The preferred terms “diplopia”, “nystagmus”, “visual impairment” and “vision blurred” in study C021 are examined for time to onset, severity, SAEs, and discontinuation, [Table 39](#). There were 174 adverse events in this pool from 154 patients. None were recorded as serious adverse events. The mean and median time to onset of this adverse event pool (that may affect vision) were 124 days and 89 days respectively. Eighty one percent (81%) of these events were judged as “mild” by the investigator with 18% judged as “moderate” severity and 1% judged as “severe”

There were 3 cenobamate discontinuations from 4 patients in with entries in this group of adverse events. One of these events was “vision blurred” the onset on study day 13, identified by the investigator as “mild” where outcome was “recovered/resolved” after discontinuation. There were two events experienced from a single patient where the adverse event entries were “nystagmus” and “diplopia”. The event of “diplopia” occurred on study day 29, was judged by the investigator as “moderate” intensity with an outcome variable entry (AEOU) as “not recovered/resolved”. The narrative report of the “diplopia” event on study day 29 does not indicate continuation of the event, although the AEOU shows “not recovered/not resolved” The second event entered for this patient was “nystagmus” where the event was judged as “moderate” intensity” with onset on study day 48 and identified as “not recovered/resolved” in the AEOU (outcome variable). The narrative indicates the outcome entry was derived from examination 2 hours after drug discontinuation. The final “diplopia” event is entered on study day 71 as “mild” with an AEOU entry of “recovered/resolved”.

Table 39 C021 Patients with Preferred Term Potentially Associated with Visual Disturbance Resulting in Study Discontinuation

Subject ID of patients with any visual disturbance term	
YKP3089C021-	(b) (6)
YKP3089C021-	(b) (6)
YKP3089C021-	(b) (6)

Reviewer Comment: Examination of terms potentially related to visual acuity dysfunction does not reveal a signal for a cenobamate associated effect on visual acuity.

Hypophosphatemia

C013-C017 OLE Has similar frequency of post baseline OORR low (< 2.5meq/L) values that are a decline from baseline, 20.4% (n=103), to that seen in C021. When ULN is set at 4.5meq/L then 17% of patients in the open label extension pool are OORR high. This is a more even distribution of low and high OORR compared to study C021.

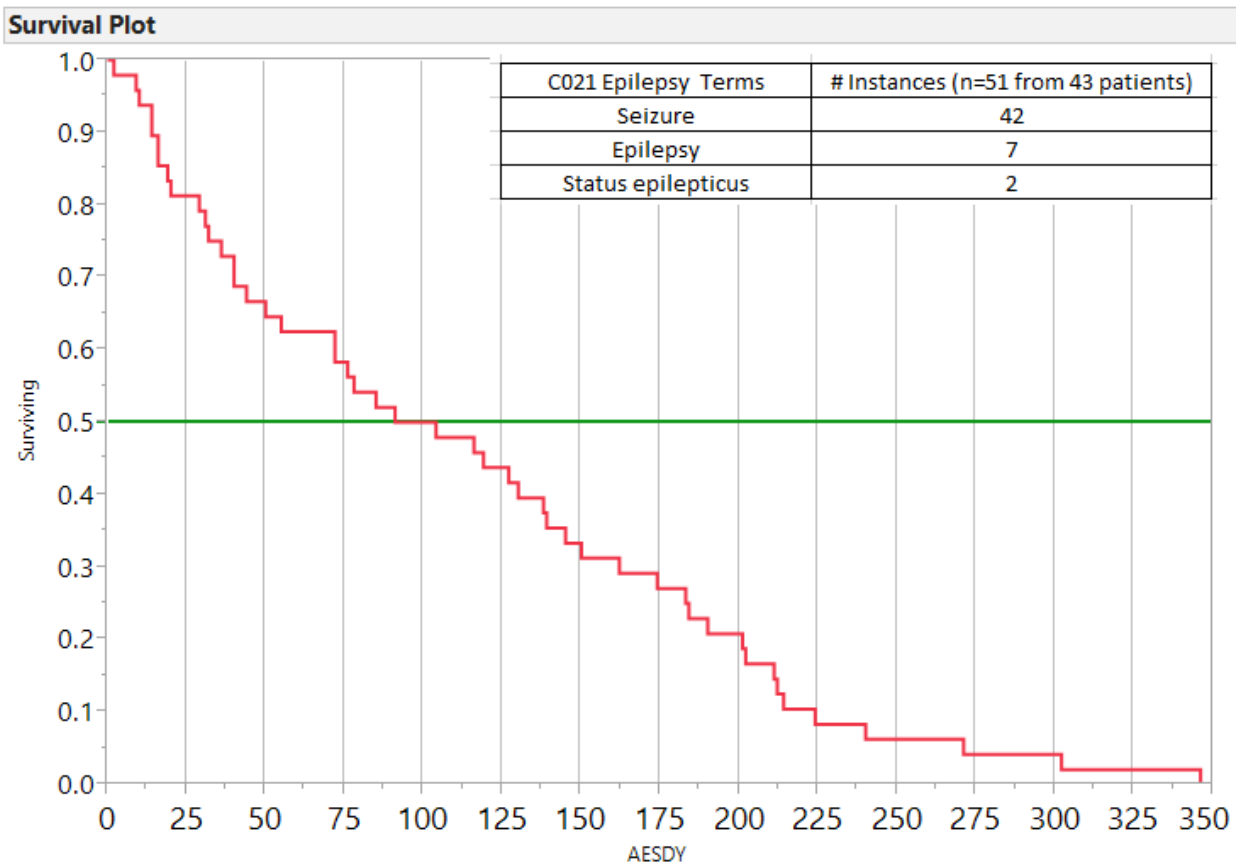
Seizure Worsening Analysis

Examination of study C013 reveals there were 4 (3.7%) epilepsy preferred terms¹³ in the placebo group and 2 (1.8%) in the 200mg cenobamate treatment arm. In addition, three of these events were status epilepticus where 2 occurred in the placebo arm and 1 in the cenobamate arm. Examination of study C017 reveals there were 3 (2.8%) epilepsy events in the placebo group, 4 (3.7%) in the 100mg arm, 2 (1.8%) in the 200mg arm and 1 (0.9%) in the 400mg arm.

In study C021 there were 43 (3.2%) patients that had an epilepsy related preferred term entry. Examination of the latency from cenobamate start to the study day of each epilepsy adverse event occurrence reveals tendency toward a steady distribution over time, see [Figure 41](#). The absence of an early cluster of seizure related adverse events is an argument against cenobamate induced worsening of the underlying epilepsy.

¹³ Reviewer Selection of epilepsy – seizure related preferred terms: Seizure, Epilepsy, Seizure cluster, Partial seizures with secondary generalization, Simple partial seizures, Atonic seizures, Autonomic seizures, Partial seizures.

Figure 41 C021, Epilepsy Related Preferred Terms, Kaplan–Meier Plot of Events Remaining by Study Day



Reviewer Comment: The distribution of epilepsy related adverse event terms in the controlled trial data reveals a trend of decline in frequency with increase in cenobamate dose. In a seizure worsening there is an expectation that frequency would increase with increasing cenobamate dose. In the examination of study C021 there was a steady occurrence over time of seizure related adverse event terms that is more consistent with breakthrough seizures seen in a refractory population than in a situation where a treatment is producing seizure worsening. If a treatment precipitated seizure worsening it is likely to be an event with a temporal relationship to the start of new treatment. This property would likely produce a cluster of events early in the course of cenobamate therapy. This profile was not observed.

8.4.6. Treatment Emergent Adverse Events and Adverse Reactions

C013 & C017 Double Blind Pool

In the pivotal study double, blind treatment pool there was a dose related increase in any TEAE

from 100mg to 400mg dose. However, the Placebo group had a percent of patients with any TEAE than the 100mg treatment arm. See [Table 40](#).

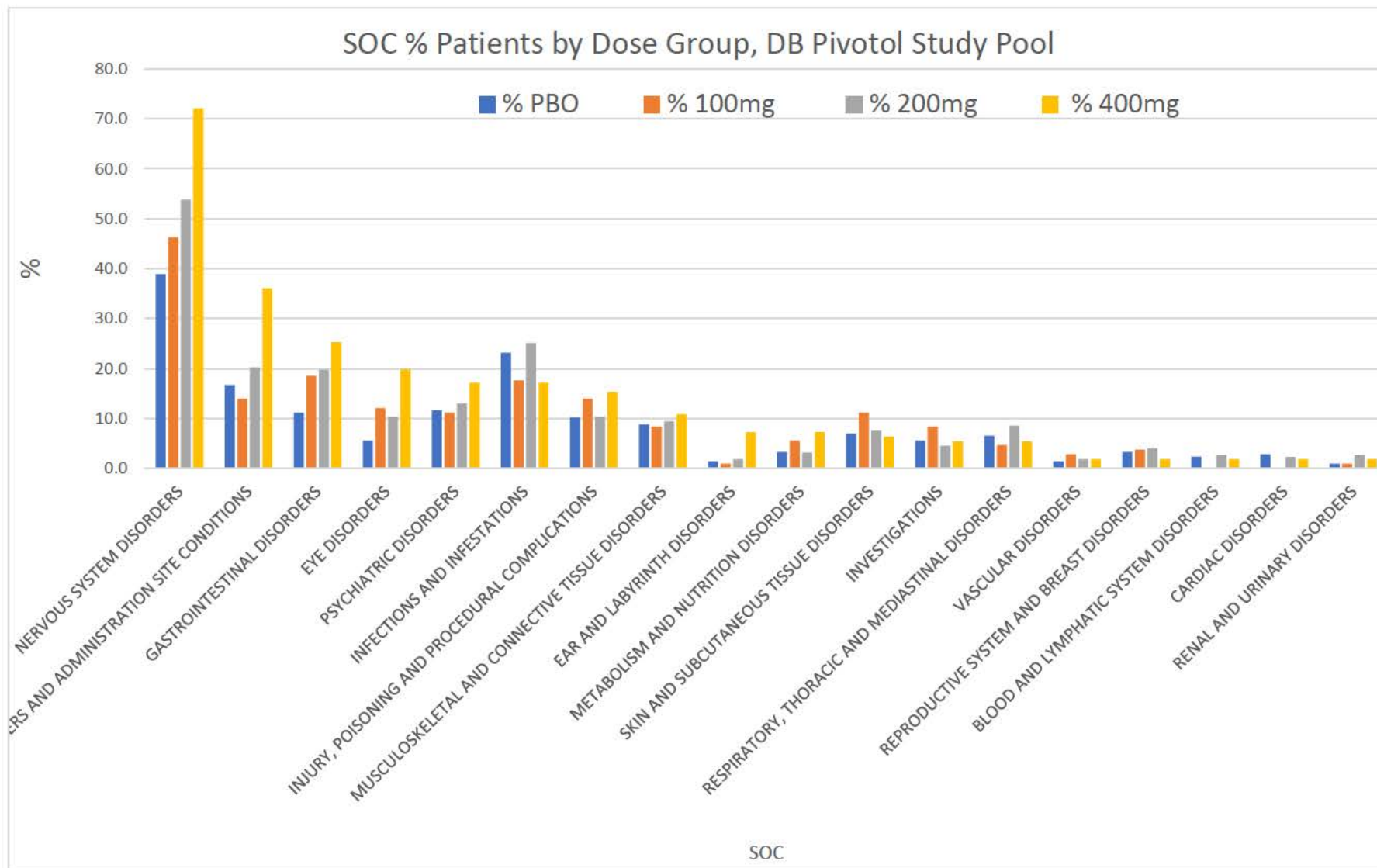
Table 40 Frequency of TEAE (instances) by Dose Group, Pivotal Studies DB Pool

	TEAE (Any, Multiple per Pt included)	# Pt TEAE	% TEAE grp
Placebo	399	149	69.0
100mg	228	70	64.8
200mg	561	172	77.1
400mg	382	100	90.1

SOC

Examination of all TEAE entries in the DB pivotal study pool reveals the most frequently populated SOC is “Nervous System Disorders” in all dose groups. There is a dose related increase in frequency of events in this SOC with a range from 39% in the Placebo treatment arm to 72% in the 400mg arm. Second in frequency of events in SOC is “general disorders and administrative site conditions where there is a dose relationship across cenobamate treatment groups. The SOC with the third most frequency proportion of adverse effects is “gastrointestinal disorders” where again there is a dose relationship, see [Figure 42](#). The frequency of individual preferred terms contained within the SOC will be discussed next.

Figure 42 % Patients in Each SOC by Dose Group, DB Pivotal Study Pool, > 2% in any Treatment Arm



Preferred Terms

Examination of TEAE in the cenobamate treatment arms of the double blind pivotal study pool reveals the most frequent adverse event is "somnolence" with a dose relationship and a maximum frequency of 37% in the 400mg treatment arm. The term "dizziness" follows, again with a dose response relationship and a maximum frequency of 33% in the 400mg treatment arm. Both of these terms are found in the SOC "nervous system disorders". The 3rd most frequent adverse event is "fatigue" with a dose response relationship and a maximum frequency of 24% in the 400mg treatment arm. This adverse event is in the "general disorders and administration site conditions" SOC. The 4th most frequent adverse event "Headache" is again in the "nervous system disorders" SOC but is without a dose response relationship. The maximum frequency of 12% is seen in the 200mg cenobamate treatment arm. "Diplopia" follows in 5th position of frequency, also in the "nervous system disorders" SOC. This adverse event has a dose response relationship with a maximum frequency of 15% in the 400mg treatment arm. In the 6th position of frequency is "nausea" from the "gastrointestinal disorders" SOC, without a dose response relationship but a maximum frequency of 9% in the 400mg treatment arm. The 7th position of frequency is "balance disorder" from the "nervous system disorders" SOC. This adverse event has a dose response relationship across cenobamate treatment. The adverse event "nystagmus" from the "nervous system disorders" SOC is the 8th most frequency adverse event associated with cenobamate treatment but does not have a dose response. The maximum frequency is 6.7% seen in the 200mg treatment arm. In the 9th position of frequency in the cenobamate treatment arms is "upper respiratory tract infection" from the "infections and infestations" SOC, without a dose response relationship but with maximum frequency seen in the 200mg treatment arm. The 10th most frequent adverse event is "constipation" from the "gastrointestinal disorders" SOC. This adverse event has a dose response relationship with the maximum frequency of 8.1% in the 400mg treatment arm. The adverse event "Vomiting" also from the "gastrointestinal disorders" SOC, follows constipation in the 11th position of frequency with a dose response. The maximum frequency of 5.4% is seen in the 400mg treatment arm. The 12th position of adverse event frequency is "nasopharyngitis" from the SOC "infections and infestations" with a dose response relationship where the maximum frequency is 4.5%. The adverse event that is 13 in order of frequency is "gait disturbance" from the "General disorders and administration site conditions" SOC. This adverse event has a strong dose response relationship where the maximum frequency is 8.1% in the 400mg arm. In 14th position of frequency is the adverse event "ataxia" from the SOC "nervous system disorders" with a dose response relationship and a maximum frequency of 6.3% in the 400mg treatment arm. In 15th position of frequency is the adverse event "back pain" from the SOC "musculoskeletal and connective tissue disorders". There is no dose response relationship and a maximum frequency of 5.4% is seen in the 400mg arm. The 16th position of adverse event frequency is observed for the term "urinary tract infection", from the SOC "infections and infestations". There is no dose response and a maximum frequency of 5.4% is seen in the 200mg arm. In 17th position of frequency is the term "diarrhoea" from the SOC "gastrointestinal disorders" with a dose response relationship and a maximum frequency of 4.5% in the 400mg dose arm. The next (18th) most frequent adverse event is "dysarthria" from the SOC "nervous system disorders" without a

dose response relationship and a maximum frequency of 7.2% seen in the 400mg treatment arm. The 19th most frequent adverse event is “fall” from the “injury, poisoning and procedural complications” SOC. This adverse event has a dose response with a maximum frequency of 3.6% in the 400mg dose group. The 20th most frequent adverse event is “vision blurred” from the “eye disorders” SOC with a dose response relationship and a maximum frequency of 3.6% in the 400mg dose arm. In 21st place from the top adverse event frequency is “decreased appetite” from the “gastrointestinal disorders” SOC without a dose response relationship and a maximum frequency of 5.4% seen in the 400mg treatment arm. The last adverse event to be covered, in position of 22nd most frequent is “vertigo” from the “ear and labyrinth disorders” SOC. This adverse event has a dose response relationship with a maximum frequency of 6.3% seen in the 400mg treatment arm. This assessment covers all adverse event where there were greater than 10 events counted among all three cenobamate treatment arms, see [Table 41](#).

From among the 22 adverse events in the prior discussion by frequency in the cenobamate treatment arms all but “upper respiratory tract infection”, “back pain”, “urinary tract infection” and “decreased appetite” had a dose response relationship. From among those remaining, with a dose response relationship, there were 5 adverse events where the placebo treatment arm had a frequency greater than one of the cenobamate arms. The placebo arm had a higher frequency than the low dose cenobamate arm for the adverse event terms “nasopharyngitis”, “gait disturbance”, and “vertigo” while the low dose (100mg) cenobamate arm was equal to the frequency in placebo for the term “ataxia”. The frequency of the adverse event “fall” was higher in the placebo arm than in any cenobamate treatment arm, see [Table 41](#).

Table 41 Pivotal Studies, C013 & C017 DB Pool, AE > 2% in Any Treatment Arm

MedDRA Category, Pivotal Studies C013 & C017 DB POOL		100mg		200mg		400mg		Placebo		Tot count
SOC	PT	n	%	n	%	n	%	n	%	Total
EAR AND LABYRINTH DISORDERS	VERTIGO	1	0.9	3	1.3	7	6.3	3	1.4	14
EYE DISORDERS	DIPLOPIA	7	6.5	15	6.7	17	15.3	4	1.9	43
	VISION BLURRED	2	1.9	5	2.2	4	3.6	1	0.5	12
GASTROINTESTINAL DISORDERS	NAUSEA	7	6.5	14	6.3	10	9	6	2.8	37
	CONSTIPATION	2	1.9	8	3.6	9	8.1	1	0.5	20
	DIARRHOEA	1	0.9	7	3.1	5	4.5	1	0.5	14
	VOMITING	2	1.9	10	4.5	6	5.4	1	0.5	19
	DRY MOUTH	1	0.9	2	0.9	3	2.7	0	0	6
	DYSPEPSIA	2	1.9	5	2.2	0	0	1	0.5	8

MedDRA Category, Pivotal Studies C013 & C017 DB POOL		100mg		200mg		400mg		Placebo		Tot count
SOC	PT	n	%	n	%	n	%	n	%	Total
	TOOTHACHE	3	2.8	2	0.9	0	0	2	0.9	7
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	13	12	31	13.9	27	24.3	16	7.4	87
	GAIT DISTURBANCE	1	0.9	6	2.7	9	8.1	3	1.4	19
	ASTHENIA	0	0	2	0.9	3	2.7	3	1.4	8
	PYREXIA	0	0	2	0.9	1	0.9	5	2.3	8
INFECTIONS AND INFESTATIONS	UPPER RESPIRATORY TRACT INFECTION	3	2.8	13	5.8	3	2.7	12	5.6	31
	NASOPHARYNGITIS	2	1.9	9	4	5	4.5	6	2.8	22
	PHARYNGITIS	1	0.9	5	2.2	0	0	1	0.5	7
	URINARY TRACT INFECTION	2	1.9	12	5.4	0	0	4	1.9	18
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	FALL	2	1.9	6	2.7	4	3.6	8	3.7	20
	CONTUSION	2	1.9	3	1.3	3	2.7	7	3.2	15
	LACERATION	1	0.9	3	1.3	1	0.9	8	3.7	13
INVESTIGATIONS	ALANINE AMINOTRANSFERASE INCREASED	1	0.9	2	0.9	4	3.6	0	0	7
	ASPARTATE AMINOTRANSFERASE INCREASED	1	0.9	2	0.9	3	2.7	1	0.5	7
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	3	2.8	2	0.9	6	5.4	2	0.9	13
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	4	3.7	5	2.2	6	5.4	6	2.8	21
	PAIN IN EXTREMITY	0	0	1	0.4	2	1.8	6	2.8	9
NERVOUS SYSTEM DISORDERS	DIZZINESS	19	17.6	50	22.4	37	33.3	33	15.3	139
	HEADACHE	11	10.2	27	12.1	11	9.9	20	9.3	69
	SOMNOLENCE	20	18.5	48	21.5	41	36.9	24	11.1	133
	BALANCE DISORDER	3	2.8	12	5.4	10	9	2	0.9	27
	NYSTAGMUS	3	2.8	15	6.7	7	6.3	1	0.5	26
	ATAXIA	2	1.9	7	3.1	7	6.3	4	1.9	20
	APHASIA	2	1.9	2	0.9	4	3.6	1	0.5	9
	DYSARTHRIA	2	1.9	3	1.3	8	7.2	0	0	13
TREMOR	0	0	7	3.1	1	0.9	3	1.4	11	
PSYCHIATRIC DISORDERS	ANXIETY	2	1.9	3	1.3	3	2.7	6	2.8	14
	CONFUSIONAL STATE	2	1.9	4	1.8	3	2.7	0	0	9
	INSOMNIA	0	0	5	2.2	1	0.9	3	1.4	9
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	DYSPNOEA	0	0	6	2.7	0	0	0	0	6

Reviewer Comment: The TEAE with a high frequency, a dose response and a frequency greater than placebo carry the greatest evidence for a causal relationship to the study drug. The top 22 adverse events in order of overall count among the cenobamate treatment arms were surveyed to assess this relationship. The majority of these events are related to CNS or gastrointestinal dysfunction and include “somnolence”, “dizziness”, “fatigue”, “headache”, “diplopia”, “nausea”, “balance disorder”, “nystagmus”, “constipation”, “vomiting”, “diarrhea”, “dysarthria”, and “vision blurred”. The events related to CNS dysfunction are more frequent early in cenobamate exposure. The majority of these adverse events occur in the first 40 days of treatment ([Figure 43](#)) and will be noted in the label section 5. These effect may be mitigated in part by the reduced dose escalation in the prescribing instructions compared to the titration rate in the pivotal studies. The adverse event terms from the SOC “gastrointestinal disorders” have a similar distribution where they are most prominent in the first 40 days of cenobamate treatment, see [Figure 44](#)

Figure 43 Adverse Event, Study Day of Onset for Preferred Terms Related to CNS Dysfunction and with a Casual Relation (discussion above), DB Pivotal Study Pool. Terms: “somnolence”, “dizziness”, “fatigue”, “diplopia”, “balance disorder”, “nystagmus”, “dysarthria”, and “vision blurred”.

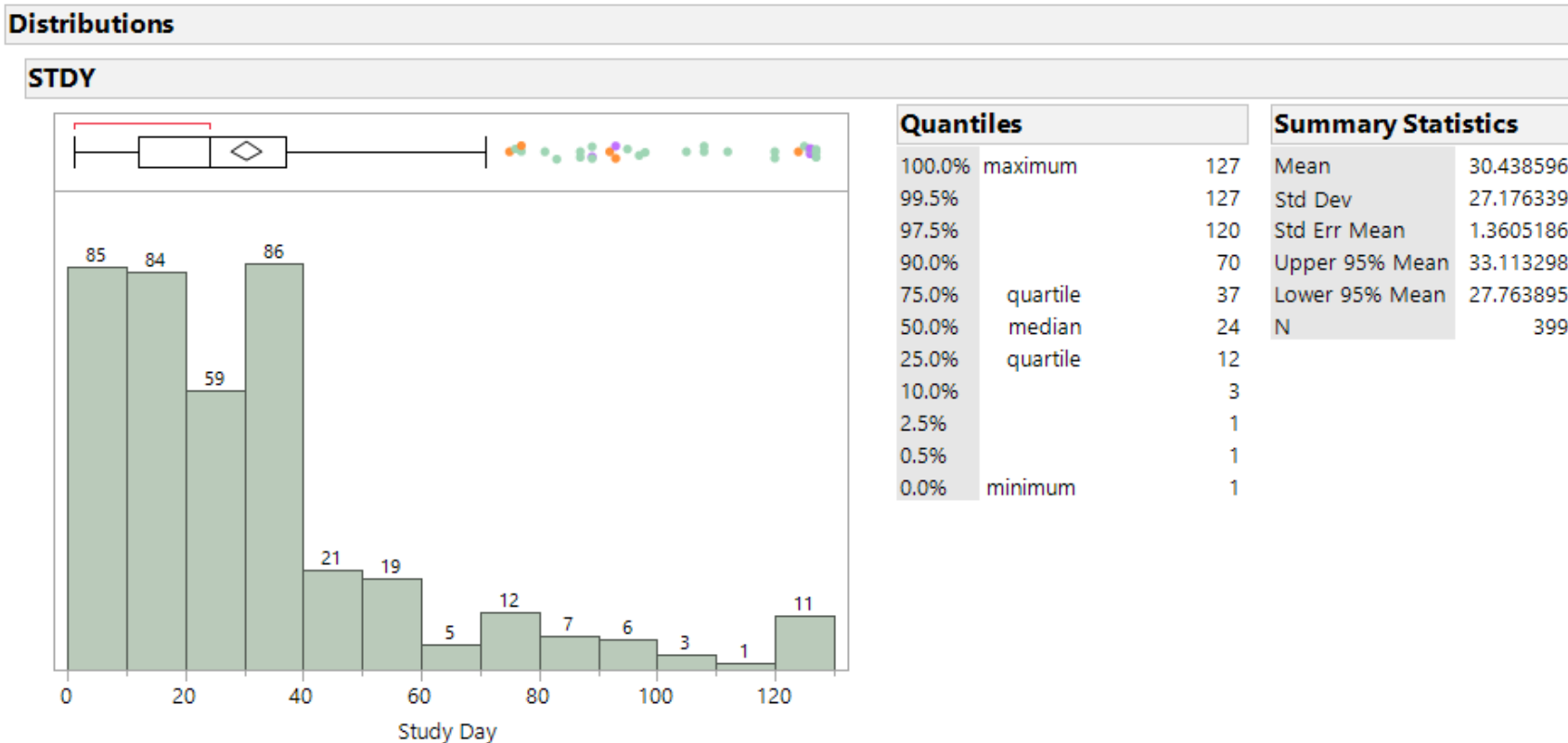
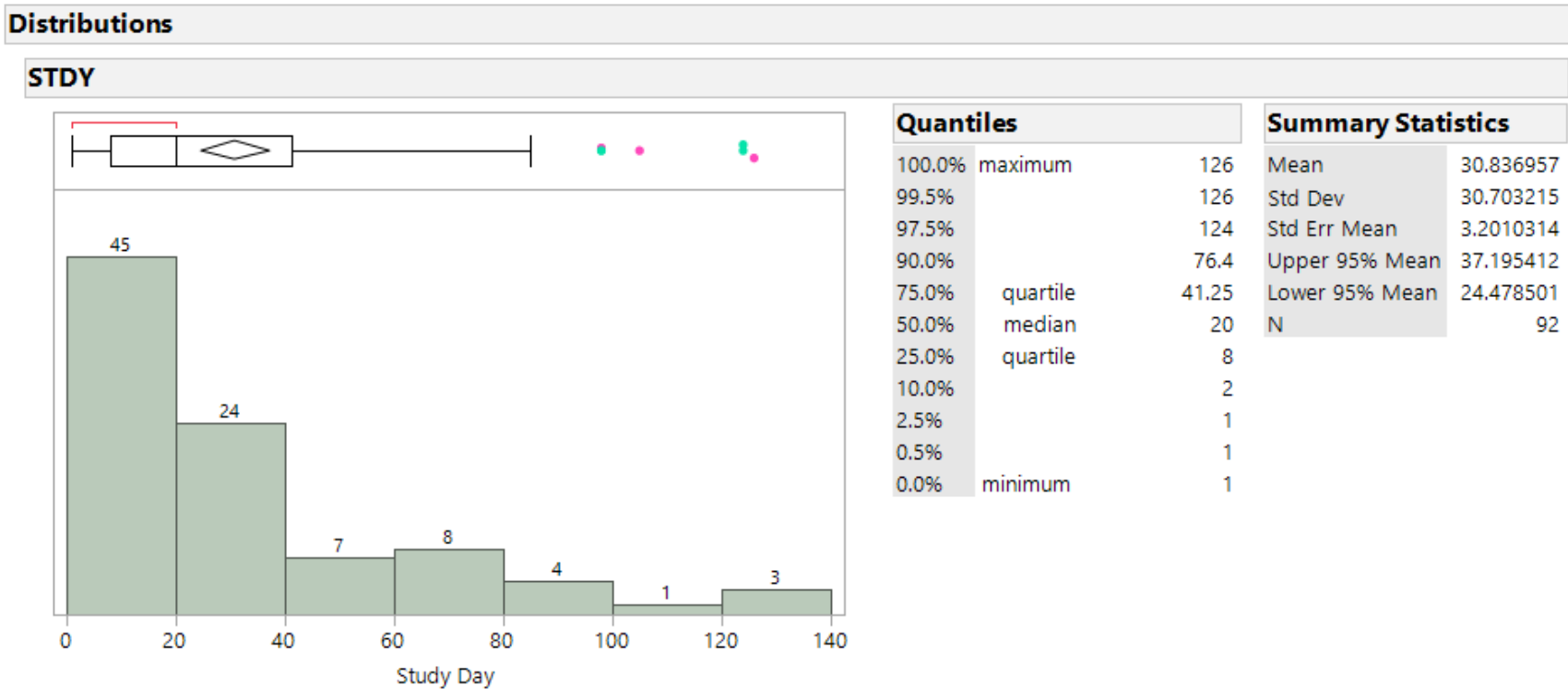


Figure 44 Adverse Event, Study Day of Onset for Preferred Terms Related to the SOC “gastrointestinal disorders” and with a Casual Relation (discussion above), DB Pivotal Study Pool. Terms: “nausea”, “constipation”, “vomiting”, “diarrhoea”, and “decreased appetite”.



C013 – C017 Open Label Pool

The TEAEs occurred during an exposure in the open label C013-C017 pool of 541132 total cenobamate treatment days. This equals 1483 patient years or an average of 2.94 years per patient in the safety dataset (positive safety flag). This open label patient pool had 505 patients (n=505)

There were 85 preferred terms from 2410 TEAE entries from 418 patients with a frequency >1%. These are shown in [Table 42](#)¹⁴.

Table 42 Studies C013 & C017 Open Label Extension Period, Adverse Events with Frequency >1.0%

PT	# Patients	%	PT	# Patients	%
Dizziness	170	33.7	Confusional state	11	2.2
Somnolence	117	23.2	Oropharyngeal pain	11	2.2
Headache	85	16.8	Weight increased	11	2.2
Fatigue	70	13.9	Abdominal pain upper	10	2.0
Diplopia	63	12.5	Aphasia	10	2.0
Upper respiratory tract infection	57	11.3	Dermatitis contact	10	2.0
Viral upper respiratory tract infection	54	10.7	Dry mouth	10	2.0
Gait disturbance	46	9.1	Gastroenteritis	10	2.0
Fall	38	7.5	Hypertension	10	2.0
Nausea	38	7.5	Neutrophil count decreased	10	2.0
Urinary tract infection	37	7.3	Seasonal allergy	10	2.0
Seizure	35	6.9	Vitamin D deficiency	10	2.0
Vertigo	35	6.9	Dyspepsia	9	1.8
Back pain	33	6.5	Gastrooesophageal reflux disease	9	1.8
Balance disorder	30	5.9	Hand fracture	9	1.8
Nystagmus	30	5.9	Pharyngitis	9	1.8
Vomiting	28	5.5	Pyrexia	9	1.8
Vision blurred	26	5.1	Toothache	9	1.8
Contusion	25	5.0	Cough	8	1.6
Constipation	24	4.8	Oedema peripheral	8	1.6
Dysarthria	24	4.8	Pneumonia	8	1.6
Ataxia	23	4.6	Sedation	8	1.6
Tremor	22	4.4	Suicidal ideation	8	1.6
Diarrhoea	21	4.2	Alopecia	7	1.4
Laceration	21	4.2	Anaemia	7	1.4
Memory impairment	20	4.0	Asthenia	7	1.4
Weight decreased	19	3.8	Concussion	7	1.4
Arthralgia	18	3.6	Ear infection	7	1.4

¹⁴ Analysis Method: C013-C017 Pool Created from ISS, 120 Day Update, Study ID C013 & C017 selected, variable APERIODC = "open label extension" with variables SF13OLF or SF17OLF = "Y", yields 3432 Rows.

PT	# Patients	%	PT	# Patients	%
Decreased appetite	18	3.6	Gastroenteritis viral	7	1.4
Pain in extremity	18	3.6	Hyperlipidaemia	7	1.4
Abdominal pain	17	3.4	Paraesthesia	7	1.4
Insomnia	17	3.4	Rhinitis	7	1.4
Anxiety	15	3.0	Skin lesion	7	1.4
Bronchitis	15	3.0	Cholelithiasis	6	1.2
Depression	15	3.0	Dental caries	6	1.2
Rash	15	3.0	Generalised tonic-clonic seizure	6	1.2
Influenza	13	2.6	Head injury	6	1.2
Irritability	13	2.6	Hypoesthesia	6	1.2
Musculoskeletal pain	13	2.6	Muscular weakness	6	1.2
Ligament sprain	12	2.4	Osteoarthritis	6	1.2
Sinusitis	12	2.4	Pruritus	6	1.2
Skin abrasion	12	2.4	Sleep disorder	6	1.2

There were 65 adverse event, preferred terms, that occurred in a frequency of greater than 1% of patients. There were 7 preferred terms that occurred in >10% of patients. These terms are “dizziness”, “somnolence”, “headache”, “fatigue”, and “diplopia”, “upper respiratory infection”, and “viral upper respiratory tract infection” with frequencies in the treatment group (n=505) of 34%, 23%, 17%, 14%, and 13% respectively. There were 982 entries for these 7 preferred terms. Forty three percent of these events occurred in the 1st six months of cenobamate treatment. Examination of the time to onset of each of the 7 preferred terms reveals that the 50% or more of adverse events associated with central nervous system dysfunction occurred in the 1st six months. The proportion of occurrences in the first six months for each of these 7 preferred terms were 67%, 61%, 57%, 50%, 18%, 13%, and 12% for “somnolence”, “fatigue”, “diplopia”, “dizziness”, “headache”, “Viral upper respiratory tract infection”, and “Upper respiratory tract infection” respectively, see [Table 43](#). The tendency of CNS adverse effect to occur earlier in treatment is also shown in xx where the timeline of occurrence for each preferred term is shown relative to the total timeline for occurrence of all 7 preferred terms with frequency >10%. This distribution is also compared to the overall distribution by study day of preferred terms with a frequency of >1%, see [Figure 46](#).

Table 43 TEAE, C013-C017 OLE Pool. Proportion of Most Frequent Events (>10% of pts) that Occurred in 1st Six Months of Cenobamate Treatment.

Preferred term (of PT>10% frequency), total 982 events	occurrences in 1st 6 months	total occurrences during study exposure	% occurrence in 1st 6 months
Somnolence	101	151	67
Fatigue	57	94	61
Diplopia	62	108	57
Dizziness	150	298	50
Headache	27	151	18
Viral upper respiratory tract infection	13	98	13
Upper respiratory tract infection	10	82	12

Figure 45 TEAE, C013-C017 OLE Pool. Distribution of Most Frequent Events (>10% of pts) by Mean Study day of Occurrence and Preferred term.

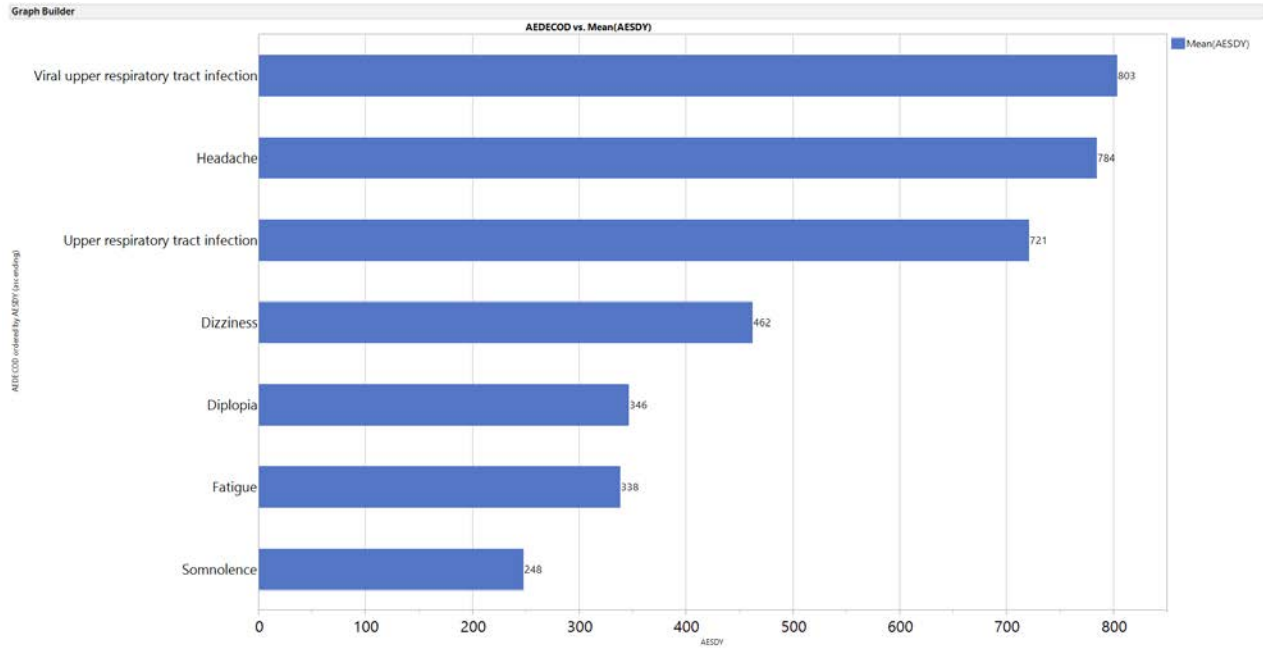
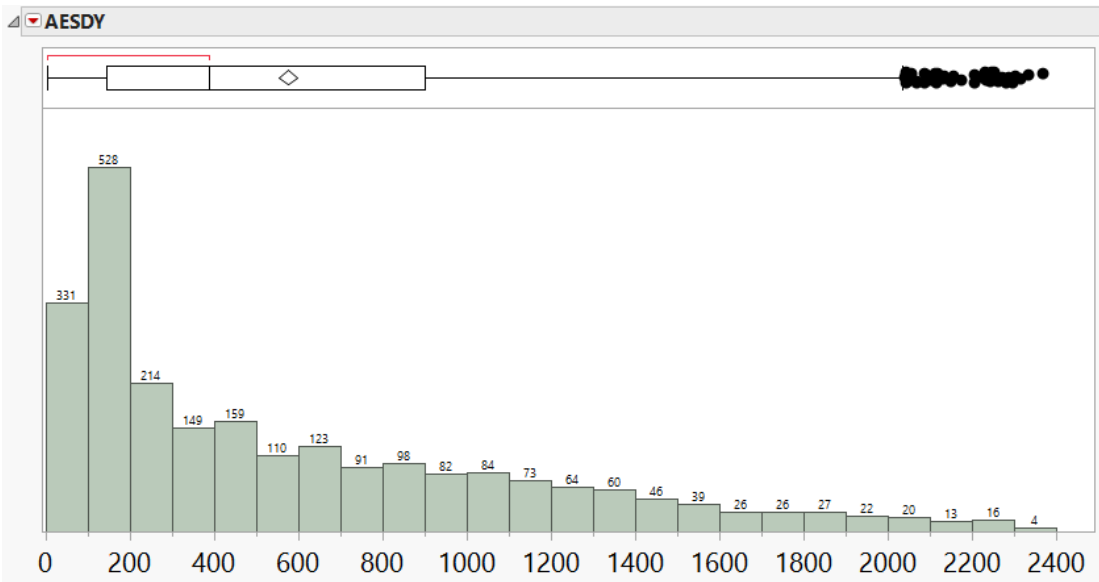


Figure 46 TEAE, C013-C017 OLE Pool. Distribution by Study Treatment Day of All Adverse Events with Preferred Terms Frequency >1% of Patients. Mean = study day 576, Median = study day 386.



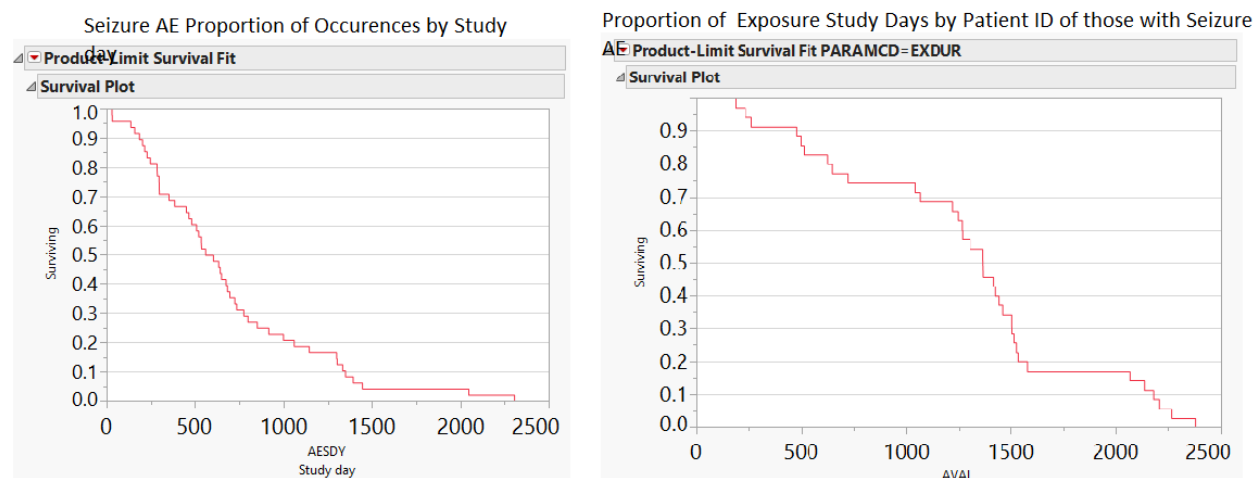
Additional CNS Dysfunction Terms

Preferred terms in the group with frequency >1% are examined. Those related to CNS dysfunction, >1% but <10% are “gait disturbance”, “fall”, “vertigo”, “balance disorder”, “nystagmus”, “vision blurred”, “dysarthria”, “ataxia”, “tremor” and “memory impairment”, “confusional state”, and “aphasia. There were 187 (37%) patients with entries for these events. Forty nine percent of all these events occurred in the first six months of cenobamate exposure.

Seizure -Preferred Term

There were 48 entries from 35 (6.9%) patients for the term seizure. There were no cenobamate discontinuations entered for these events although there are 4 entries for “dose reduced” and 3 for “not applicable” entered. These events do not appear related to lack of efficacy associated with early occurrence or loss of efficacy, related to duration of treatment, see the Kaplan–Meier plot for occurrence of event by study day. The maximum exposure in days by patient is also shown for comparison, see [Figure 47](#).

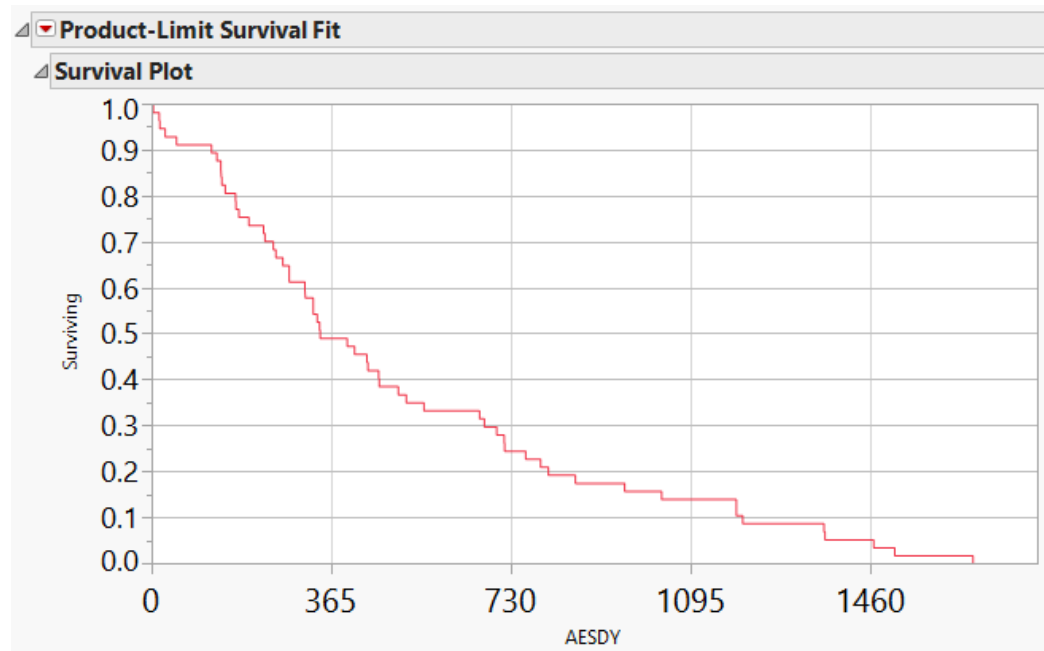
Figure 47 Study C013-C017, TEAE “Seizure”, Kaplan–Meier plot, 35 Patients, Proportion of Events by Study Day, Exposure Days by Patient ID.



Psychiatric Terms >1%

There were 57 entries from 46 (9.1%) patients with the preferred terms “anxiety (3%)”, “depression (1.6%)”, “irritability (2.6%)”, and “suicidal ideation (1.8%)”. None of these terms was entered as an SAE and cenobamate was withdrawn from 4 patients. three of the four withdrawals were for “depression” and the remaining for “anxiety”. Approximately half of these adverse events occur in the first year with 80% occurring in approximately the first 2 years of treatment, see [Figure 48](#). The adverse events of suicidal ideation have a predominance of occurrence in the first year of treatment where 7 of 9 events occurred between day 169 and 396.

Figure 48 Study C013-C017, TEAE, Kaplan–Meier plot, Proportion AE Remaining by Study day: Psychiatric Preferred Terms “anxiety”, “depression”, “irritability” and “suicidal ideation”.



Gastrointestinal Disorders Terms

The terms “constipation”, “abdominal pain” and “gastroenteritis” are examined as possibly related to the high frequency of the adverse event “appendicitis”. These terms may reflect change in gastrointestinal motility or tendency for infection. There were 62 entries for these terms from 51 patients. There was one cenobamate withdrawal for an event of “constipation” and one entry as an SAE for the term “gastroenteritis”. Thirty for entries were judged by the investigator as “mild” and 24 as “moderate” by the investigator. Four were judged as “severe”. These were 3 entries for “abdominal pain” and one entry of “constipation”. *Constipation is present in proposed labeling in the adverse event table.*

Potential Hypersensitivity Events

Potential hypersensitivity events are captured by examination of the “immune system disorders” and “Skin and subcutaneous tissue disorders” SOCs. In these two categories there were 116 entries from 76 (15%) patients. In this group there were entries from 42 preferred terms where 15 terms with 51 entries from 40 (8%) patients were selected as potentially related to hypersensitivity. Terms were recoded to consolidate similar events. All dermatitis terms were recoded to “dermatitis” and all rash terms were recoded to “rash” see [Table 44](#). From among these terms none was entered as an SAE. There were 3 cenobamate withdrawals,

one each for “angioedema”, “pruritus”, and “rash”. The “angioedema” and “rash” events were judged as “mild” severity and the “pruritus” was judged as “moderate” severity. *Assessment: There were 8% of patients overall with these terms but no SAEs for potential hypersensitivity in this OLE safety dataset. The term “angioedema” is of concern to possible relationship to DRESS but this was judged as mild but did result in drug withdraw. These findings are consistent with the hypersensitivity signal that has been identified.*

Table 44 C013-C017 OLE, TEAE, Potential Hypersensitivity Preferred Terms, Action Taken With Treatment, # Entries. (none Entered as SAEs)

PT	# Event Entries	Action Taken with Treatment	Severity
Angioedema	1	DRUG WITHDRAWN	Moderate
Dermatitis	11	DOSE NOT CHANGED	Mild
Dermatitis	2	DOSE NOT CHANGED	Moderate
Dermatitis	1	NOT APPLICABLE	Mild
Dermatitis	1	NOT APPLICABLE	Moderate
Drug eruption	1	DOSE NOT CHANGED	Moderate
Erythema	1	DOSE NOT CHANGED	Mild
Hypersensitivity	1	DOSE NOT CHANGED	Mild
Pruritus	6	DOSE NOT CHANGED	Mild
Pruritus	1	DRUG WITHDRAWN	Moderate
Rash	20	DOSE NOT CHANGED	Mild
Rash	1	DOSE REDUCED	Moderate
Rash	1	DRUG INTERRUPTED	Moderate
Rash	1	DRUG WITHDRAWN	Moderate
Rash	1	NOT APPLICABLE	Mild
Skin haemorrhage	1	DOSE NOT CHANGED	Mild

Reviewer Comment: TEAE seen in C013-C017 Pooled OLE reveal adverse event frequencies that are in similar to those identified in the double-blind pivotal studies. Terms related to CNS dysfunction are most common and have a predominant occurrence within the first six months of cenobamate treatment. The adverse events in the psychiatric disorder SOC are consistent with the class effect of AEDs and do not appear to demonstrate a notable departure from the existing signal. The “seizure” adverse events are not an independent safety signal. These events are not a notable departure from the background occurrence of seizure in a refractory epilepsy population. The gastrointestinal events of “constipation”, “abdominal pain” and “gastroenteritis” are not of frequency and intensity to indicate a novel safety signal in cenobamate treatment. The hypersensitivity associated events are in alignment with a tendency for activation of hypersensitivity.

C021

The TEAEs in study C021 occurred during an open label exposure total of 532855 days of cenobamate treatment. This equals 1460 patient years or an average of 1.09 years per patient

in the safety dataset (positive safety flag 1399 patients¹⁵).

In study C021, 1154 patients had 4814 TEAEs from 782 preferred terms over a maximum span of 748 treatment days on cenobamate (see study [C021 Exposure, section 8.2.1](#)). This analysis captures all TEAEs at any dose from initiation of cenobamate treatment. The mean and median modal dose were 200mg and 206 mg respectively. The duration of exposure and modal dose distribution may be seen in [section 8.2.1, C021 Modal Dose](#).

TEAE Preferred Terms with a Frequency >10%

There were 4 adverse events with a frequency greater than 10%. These include the preferred terms “somnolence”, “dizziness”, “fatigue”, and “headache” with frequencies of 28%, 25%, 17% and 13% respectively, see [Table 45](#).

TEAE Preferred Terms with Frequency > 4%

Additional frequent events include “Viral upper respiratory tract infection”, “Nausea”, “Upper respiratory tract infection”, “diplopia”, “balance disorder”, “constipation”, “vision blurred”, “diarrhoea”, and “fall” at frequencies of 8%, 7%, 7%, 6%, 6%, 4%, 4%, 4%, and 4% respectively. These preferred terms are similar to those seen in the double-blind treatment intervals of studies C013 and C017 as well as the open label extension of these studies. An analysis is performed to assess the severity and temporal relationship of the events with a frequency between 4% and 10%. There were 2 serious adverse events of “balance disorder” both judged as severe by the investigator with an average study day occurrence of 112 days. This represents 2.5% of all 79 “balance disorder” TEAEs. Three additional “balance disorder” events were judged as severe by the investigator. Constipation has a high frequency seen in temporal relationship to cenobamate treatment.

There were 59 (4.4%) patients with an entry for the preferred term “constipation”. Forty eight (81%) of these were judged “mild” by the investigator, 10 were judged as “moderate”, including the SAE, and 1 was judged as severe, see Section [8.4.5, Significant Adverse Events](#),

Constipation

There were 79 (5.9%) patients with an entry for the preferred term “balance disorder”. The mean study day of occurrence for these “balance disorder” events was day 105 while the mean and median of those 3 non-SAE events judged as “severe” intensity by the investigator were 72 and 66 respectively.

There were 57 (4.2%) patients with an AE of “diarrhoea” where 41 (72%) were judged as “mild” and 16 judged as moderate by the investigator. None were serious adverse events (SAE).

There were 83 (6.2%) patients with an AE of “diplopia” where 58 (70%) were judged as “mild” by the investigator” and 25 judged as moderate in severity by the investigator. None were SAEs. The mean and

¹⁵ Safety dataset derived from the SAFFL variable of the ADSL initial 11/21/18 submission

median study day of those “diplopia” events judged as “moderate” intensity by the investigator were 91 and 94 days respectively.

There were 55 (4.1%) patients with a “fall” event. From among these 3 were SAEs. The study day of occurrence of these three SAEs were 14, 55 and 159. Thirty-three (60%) events were judged as “mild” by the investigator (although 1 was an SAE) while 19 were judged as “moderate” intensity and 3 were judged as “severe” intensity.

There were 96 (7.1%) patients with an adverse event of “nausea”, where 71 were judged as “mild” by the investigator, 23 were judged as “moderate” and 2 as “severe” intensity. None was an SAE. The two “severe” adverse events of “nausea” were early after the start of cenobamate treatment with a mean onset of study day 61.

There were 93 (6.9%) patients with an adverse event of “Upper respiratory tract infection” where 75 were judged by the investigator as “mild” and 17 as “moderate”. None was an SAE. Mean and median time to onset of all “upper respiratory tract infection” events were 135 and 89 days respectively.

There were 41 (3.1%) patients with an adverse event of “urinary tract infection” where two were SAEs, one each occurring on study day 46 and 96. These were judged by the investigator as “Moderate” and “severe” respectively.

There were 25 (1.9%) patients with “urinary tract infection”, 61% were judged as mild and 15 judged as “moderate”.

There were 104 (7.7%) patients with an event of “Viral upper respiratory tract infection” where 85 events were judged as “mild” by the investigator and 19 judged as “moderate”. None was an SAE. The mean and median time to onset of all “Viral upper respiratory tract infection” adverse events were 133 and 98 days respectively.

The final category of frequent TEAE’s > 4% is “vision blurred”. There were 56 (4.2%) patients with an adverse event of “vision blurred” where 53 were judged as “mild” by the investigator, 2 were judged as “moderate” intensity and 1 was judged as “severe”. The mean and median time to onset of the “vision blurred” adverse event were 118 and 86 days respectively. None was an SAE.

TEAE Frequency > 1%

Table 45 Study C021, Any TEAE >1%

SOC	Preferred Term	# Patients	% Patients
Ear and labyrinth disorders	Vertigo	29	2.2
Eye disorders	Diplopia	83	6.2
	Vision blurred	56	4.2
Gastrointestinal disorders	Nausea	96	7.1
	Constipation	59	4.4
	Diarrhoea	57	4.2
	Vomiting	48	3.6

SOC	Preferred Term	# Patients	% Patients
	Toothache	17	1.3
	Abdominal pain upper	16	1.2
General disorders and administration site conditions	Fatigue	224	16.7
	Gait disturbance	47	3.5
	Asthenia	34	2.5
	Pyrexia	15	1.1
Infections and infestations	Viral upper respiratory tract infection	104	7.7
	Upper respiratory tract infection	92	6.8
	Urinary tract infection	41	3.1
	Influenza	31	2.3
	Gastroenteritis	25	1.9
	Bronchitis	18	1.3
	Sinusitis	16	1.2
Injury, poisoning and procedural complications	Fall	55	4.1
	Laceration	34	2.5
	Contusion	25	1.9
	Ligament sprain	24	1.8
	Head injury	17	1.3
Investigations	Weight decreased	38	2.8
	Weight increased	20	1.5
Metabolism and nutrition disorders	Decreased appetite	29	2.2
	Hyponatraemia	15	1.1
Musculoskeletal and connective tissue disorders	Back pain	29	2.2
	Arthralgia	21	1.6
Nervous system disorders	Somnolence	380	28.3
	Dizziness	329	24.5
	Headache	175	13
	Balance disorder	79	5.9
	Seizure	52	3.9
	Ataxia	49	3.6
	Tremor	32	2.4
	Dysarthria	29	2.2
	Nystagmus	30	2.2
	Lethargy	20	1.5
	Memory impairment	20	1.5
	Disturbance in attention	17	1.3
	Aphasia	16	1.2
	Hypoaesthesia	15	1.1
Psychiatric disorders	Anxiety	34	2.5
	Depression	28	2.1
	Irritability	28	2.1
	Insomnia	27	2
	Confusional state	15	1.1
	Suicidal ideation	15	1.1
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	23	1.7
	Nasal congestion	17	1.3
	Cough	15	1.1

SOC	Preferred Term	# Patients	% Patients
Skin and subcutaneous tissue disorders	Pruritus	31	2.3
	Rash	23	1.7
	Dermatitis contact	18	1.3
Vascular disorders	Hypertension	18	1.3

Select TEAE that have a frequency 1%≥ are examined:

With the following methodology; the preferred terms are examined for content of special interest based on the potential relationship to a serious medical condition that if related to study drug treatment may be of special concern. In addition, the preferred terms are examined for potential relationship to submission specific concerns of hypersensitivity and short QT – cardiac related events. Preferred terms from this group that are entered as SAEs will also be captured and selectively examined. Examination of the subset of preferred terms with a frequency ≤1% yields 60 terms from 219 patients with a total of 234 adverse event instances. This examination captured 28 preferred term entries with only one instance.

From among this subset of the C021 TEAE adverse events the most frequent was “ alanine aminotransferase increased” (1%), with no SAEs, “eosinophilia” occurred in 12 patients (1%) with no SAEs or associated cenobamate discontinuation. Eleven patients experienced “dyspnea” occurred in 11 patients with no SAEs and 1 drug discontinuation, see above discussion in study C021 “preferred terms of interest”.

There were 10 patients who experienced pneumonia where 5 occurred as an SAE (1 patient, YKP3089C021- (b)(6) had 2 (SAE) episode of pneumonia). The first event was judged as mild by the investigator on study day 56. A second event judged as “moderate” severity occurred on study day 74. No clear etiology is identified, cenobamate was continued until day 713. Examination of clinical laboratory studies does not reveal evidence of myelosuppression. A second SAE entry for pneumonia occurred on study day 4. This is early for a physiologic relationship to cenobamate. The investigator judged the event as “mild” intensity and cenobamate was continued until study day 92. The patient maximum dose began on study day 71 as 200mg. The third patient with an SAE of pneumonia had this adverse event on study day 161, entered as “severe” intensity but cenobamate was continued. No underlying laboratory abnormalities were identified that may be associated with pneumonia such as evidence of myelosuppression. The patient continued in the study until day 379 and had a maximum cenobamate dose of 400mg. There were 2 additional cases of pneumonia as an SAE. These occurred later on the treatment timeline reducing causality based on temporal relationship. The times to onset in one of the two cases was at 1 year and in the second of the two at 14 months. Cenobamate was continued. In the remaining 7 cases the events were judged as “mild” or “moderate” intensity and cenobamate was continued unchanged in all. The time to onset in these remaining cases ranged from 76 days to 694 days.

There were 8 patients who experience an adverse event of “rash papular” where in 3 cases the

event was an SAE. In two of these three cases cenobamate was discontinued the time to onset in the three cases was 41 days, 139 days and 317 days. The case that had TTO of 41 days there was a skin biopsy performed that revealed “spongiotic reaction with dermal perivascular infiltrate and eosinophilia, consistent with a drug reaction”. The cenobamate dose at time of onset was 50mg a day. Escalation from 25mg to 50mg had occurred on study day 28. The remaining two “rash papular” cases entered as an SAE were judged as “mild” intensity by the investigator and will be called case 1 and case 2. Case 1 occurred on study day 139 while the patient was on 200mg of cenobamate, the patient reported feeling itchy and hot. The investigator judged the event as “mild” severity and the event resolved in 5 days after cenobamate discontinuation. Case 2 occurred on study day 317 while the patient was taking 400mg of cenobamate. The patient had a bilateral flank papular eruption progressing to the lower limbs, there was no other evidence of systemic hypersensitivity. The event resolved 12 days after discontinuation of cenobamate.

There were 7 patients who experienced a TEAE of “erythema”, one entered as an SAE. In this case the event was judged by the investigator as “moderate” severity and cenobamate was discontinued when the patient developed “facial redness across cheeks, nose, chin and forehead” on study day 22 while receiving 25mg of cenobamate. The event resolved approximately 1 month after drug discontinuation. The remaining six TEAEs of erythema were judged as “mild” severity by the investigator and cenobamate was continued.

There were 7 patients who experienced “hyperkalemia” where none was an SAE but cenobamate was discontinued in one case where there was an associated elevation of ALT and AST. Potassium was found to be elevated to 6.3meq/L on study day 60 at a cenobamate dose of 100mg, with an associated elevation of ALT to 16 x ULN and AST to 2.8 x ULN. The narrative indicates last dose of cenobamate on study day 65 with normal potassium and AST values obtained at an unscheduled visit on study day 66 and ALT improved to a level of 2.7 x ULN. The remaining six patients with an event of “hypokalemia” had severity judged as “mild” by the investigator and cenobamate continued in all cases. The median time to the “hypokalemia” events was 77 days.

There were six patients who experienced a TEAE of “urticaria” where one was entered as an SAE and cenobamate was discontinued in 3 of the 6 patients. The SAE occurred on study day 2 after 2 doses of cenobamate 12.5mg. the patient developed an urticarial body rash and recovered 2 days after drug discontinuation. This report is also discussed above in section 8.4.2 Serious Adverse Events, [Study C021](#). For reference the two cases of the TEAE “urticaria” will be designated case 1 and 2. In case 1 (YKP3089C021-(b) (6)) the event occurred on study day 10 at a cenobamate dose of 12.5mg. The patient experience “allergic reaction- itchy skin rash and hives to right side of face”. The event was judged as “moderate” severity by the investigator. Cenobamate was discontinued and the event resolved 10 days later. In case 2 the patient experienced “moderate urticaria on trunk, hip and extremities” on study day 5 at a cenobamate dose of 12.5mg. The patient was treated with Chrolopyramin and Methylprednisolone and recovered from the event in 2 days. In the remaining 3 cases of a TEAE

of “urticaria” the investigator judged the severity as “mild”. Cenobamate was continued in these three cases. These cases, one each, had onset on study days 50, 95 and 344.

There were 4 patients who experiences a TEAE of “deep vein thrombosis” where one was entered as an SAE. The patient who experienced an SAE (YKP3089C021-^{(b) (6)}) also had a serious cardiac adverse event discussed in [section 8.4.4 Cardiac Adverse Events](#). The initial medical event on study day 185 at a cenobamate dose of 250mg, was a “complete heart block”, upon hospitalization the patient was also found to have a popliteal venous thrombosis, also on study day 185. The patient was treated with apixaban and continued in the study on cenobamate treatment until study day 448. The patient reached a dose of cenobamate 250mg on study day 132. There is no further discussion on recovery from the venous thrombosis in the narrative. The remaining 3 patients with “deep vein thrombosis” had the event judged as “mild” severity by the investigator and cenobamate dose was not changed. The mean and median study day of onset were 279 and 232 days respectively. *These events are loosely coupled in temporal relationship to onset of cenobamate treatment between day 232 – 279 but appear to be sporadic background events with an uncertain relationship to study drug.*

There were 4 patients with a TEAE of “rash maculo-papular”. In one case cenobamate was discontinued and in a second the event was entered as an SAE. In the case of the SAE (patient YKP3089C021-^{(b) (6)}) the event occurred on study day 62, cenobamate was discontinued and the severity was judged as “moderate”. This event is discussed more fully in [Study C021 section 8.4.2 Serious Adverse Events](#). The second case with a disposition event was patient YKP3089C021-^{(b) (6)} who developed a rash on study day 248 judged as “mild” severity by the investigator. Cenobamate dose was 150mg. The patient was treated with topical hydrocortisone cream and recovered 8 days after discontinuation of cenobamate.

There were 3 TEAE events of “dermatitis allergic”. From among these entries there was one entered as an SAE with drug discontinuation, patient YKP3089C021-^{(b) (6)}. This event occurred on study day 67 with a 100mg dose of cenobamate. Over approximately 5 days the patient noted progression of erythematous lesions from the right gluteal area to the abdominal and thoracic region. There were no other signs or symptoms. The findings resolved over approximately 1 month.

There were 3 TEAE of “hypernatraemia” where one was also entered as an SAE, full discussion not previously captured in the discussion of C021 SAE. This patient, YKP3089C021-^{(b) (6)} developed hypernatraemia on study day 246 in the context of a PMH of development delay and treatment for recurrent migraine headache. Headache was treated with dihydroergotamine and intravenous methylprednisolone. The patient recovered from the SAEs of hypernatraemia and hypokalemia on study day 252. The remaining two TEAEs of “hypernatraemia” occurred one each on study day 211 and 272. Cenobamate was continued in all three cases of a TEAE (including the SAE) of “hypernatraemia”, all were judged as “mild” severity by the investigator.

The remaining TEAEs in study C021 with frequency $\leq 1\%$ that are entered as an SAE are events

with only a single occurrence (0.07%). There were 10 events in this category. Eight of these events were captured as an [SAE in study C021 in section 8.4.2](#) or [Section 8.4.1 Deaths](#). There were two events that were SAEs, not previously captured. The first was an SAE of “serositis” experienced by patient YKP3089C021-^{(b) (6)} on study day 140, on a cenobamate dose of 150mg. The narrative report indicates there was a prodrome of fatigue and not feeling well, possibly dating to the initiation of cenobamate. The patient presented to the emergency room with fever and pleuritic chest pain and was found to have a pericardial rub. A pleural and pericardial effusion were identified on imaging. CRP was highly elevated at 283mg/L (reference range <3mg/l) and hemoglobin 8.7g/dl. Cenobamate was discontinued. The investigator indicates this adverse event may be confounded by *concomitant treatment with dasatinib*, (SPRYCEL) where pleural and pericardial effusions have been seen in clinical trials. The patient improved at the next assessment 9 days after cenobamate was discontinued with decline of CRP to 84mg/L and Hb increased to 10.9g/dL. The next event captured in the low frequency TEAE assessment where events were also entered as SAEs was a case of “myelopathy”. This event was related to a seizure related injury and fall.

The remaining events with frequency $\leq 1\%$, identified as special interest, had no associated SAEs, see [Table 46](#).

YKP3089C021-^{(b) (6)} PT Alanine aminotransferase increased: This occurred during an SAE of headache, cenobamate was withdrawn. The final scheduled laboratory study was on study day 59, the ALT was elevated at 194 (5.9 X ULN). The ALT value associated with the SAE, emergency room visit for headache) on study day 72 is not reported. Resolution of this laboratory abnormality is also not reported.

YKP3089C021-^{(b) (6)} PT angioedema: On study day 4, while on cenobamate 12.5mg, the subject experienced a TEAE of “mild” severity “angioedema”. The study drug was withdrawn. The subject was treated with Loratadine and the subject recovered from the event on study day 24.

YKP3089C021-^{(b) (6)} PT “dermatitis allergic”: this 36 yo Eurasian female developed a TEAE of “dermatitis allergic” on study day 3 of treatment with cenobamate 12.5mg. the patient developed a mild Allergic reaction-skin rash over upper chest. Physical exam 4 days after discontinuation of study drug revealed no of the rash or other hypersensitivity signs.

YKP3089C021-^{(b) (6)} PT drug eruption: a 61 yo Caucasian male developed a mild rash consistent with drug eruption on study day 123 while taking 100mg cenobamate. Physical exam and laboratory revealed no evidence of other hypersensitivity signs or symptoms. On study day 152 the patient recovered from the rash.

YKP3089C021-^{(b) (6)} PT Eosinophil count increased: 28-year-old Caucasian male developed elevated absolute eosinophil count on study day 84 while on cenobamate 200mg. This occurs a background history of breakthrough seizure and pneumonia that occurred on study day 4.

Previously on study day 10, the subject experienced dermatitis on hands and arms due to seasonal dry skin and dermatitis on groin due to bacterium. Study drug was withdrawn on study day 91 due to the event of eosinophil increased.

YKP3089C021- (b) (6) PT eosinophilia: a 38 yo Hispanic male was found to have a TEAE of eosinophilia during a hospitalization for lower gastrointestinal bleeding on study day 42 while taking cenobamate 50mg. The patient also is reported to have elevated liver function studies. The hospital personnel concluded the LFT elevation was due to concomitant valproic acid. The values for liver function studies and eosinophils are not reported. Last dose of cenobamate was on 4/5/17.

YKP3089C021- (b) (6) PT hyperkalemia: see discussion above on [7 patients with TEAE of hyperkalemia](#).

The remaining cenobamate withdrawals were due to TEAEs with preferred terms potential associated with hypersensitivity. Pharmacovigilance for any hypersensitivity features was very high in study C021. The study was directed at examination of the relationship of reduced titration rate and frequency of DRESS syndrome. An overview of these remaining 11 cenobamate withdrawals will be included in [section 8.5 Submission Specific Safety Issues, DRESS Risk](#).

Remaining are 178 TEAE entries from 147 patients of the group with a preferred term frequency $\leq 1\%$, not including SAEs, or cenobamate withdrawal events. There were 46 preferred terms in this group. There were 10 or more instances of the terms “Alanine aminotransferase increased”, “eosinophilia”, “syncope”, and “dyspnea”. From among these 178 TEAEs there were 147 (83%) judged by the investigator as “mild” severity and 31 (17%) judged as “moderate” severity.

Table 46 Study C021, Select TEAE of Interest from All AE Frequency $\leq 1\%$ Including SAE Status

Preferred Term	Patient Count	SAE count	Preferred Term	Patient Count	SAE Count
Alanine aminotransferase increased	13	0	Drug hypersensitivity	2	0
Eosinophilia	12	0	Hypersensitivity	2	0
Dyspnoea	11	0	Acute myocardial infarction	1	1
Aggression	11	1	Acute respiratory failure	1	1
Pneumonia	10	5	Atrioventricular block complete	1	1
Eosinophil count increased	9	0	Cerebral haemorrhage	1	1
Rash papular	8	3	Laryngospasm	1	1
Rash erythematous	8	0	Major depression	1	1
Erythema	7	1	Myelopathy	1	1
Hyperkalaemia	7	2	Serositis	1	1
Urticaria	6	1	Sudden death	1	1
Hypokalaemia	6	0	Visual acuity reduced	1	1

Preferred Term	Patient Count	SAE count	Preferred Term	Patient Count	SAE Count
Neutrophil count decreased	6	0	Abasia	1	0
Rash macular	6	0	Acute prerenal failure	1	0
Syncope	6	0	Angioedema	1	0
Urinary retention	6	0	Atrial fibrillation	1	0
Agitation	4	0	Blood creatinine increased	1	0
Anaemia	3	0	Cerebral haematoma ²³⁴	1	0
Aspartate aminotransferase increased	5	0	Hostility	1	0
Epistaxis	4	0	Neurodermatitis	1	0
Hot flush	5	0	Neuropathy peripheral	1	0
Deep vein thrombosis	4	1	Paralysis	1	0
Rash maculo-papular	4	1	Peripheral vascular disorder	1	0
Pruritus generalised	4	0	Pharyngeal erythema	1	0
Thrombocytopenia	4	0	Rash generalised	1	0
Transaminases increased	4	0	Rash morbilliform	1	0
Dermatitis allergic	3	1	Rash pruritic	1	0
Hypernatraemia	3	1	Skin burning sensation	1	0
Dermatitis atopic	3	0	Skin discolouration	1	0
Drug eruption	3	0			
Hallucination	2	0			

An assessment of the median time to TEAE preferred term occurrence in study C021 and the associated frequency of the preferred terms is shown in [Figure 49](#) and [Figure 50](#). This purpose of this assessment is to identify the temporal relationship between start of cenobamate treatment and onset of the adverse effect. The basis of interpretation is that a shorter temporal relationship (tighter coupling between onset and event) is supportive of causality compared to events that occur sporadically scattered across the study timeline. This assessment was partially informative. Several events of unexpected causal relationship occurred in close relationship to start of treatment. These events were “neuropathy peripheral”, “skin discoloration”. These are adverse reactions that characteristically have a duration to manifestation longer than 10 days. Adverse events that occurred where a close temporal relationship increases plausible causality were “pharyngeal erythema” and “skin burning sensation”, that may be a hypersensitivity phenomenon. Adverse events seen to have a median temporal relationship with a maximum of 80 days ([Figure 49](#)), where causal association is plausibly increased by this relationship, were “abasia”, “rash maculo-papular”, “rash erythematous”, “dermatitis atopic”, “aspartate aminotransferase increased”, “aggression”, “rash papular”, “agitation”, and “alanine aminotransferase increased”. These are events associated with the hypersensitivity potential of cenobamate or the central nervous system dysfunction seen with cenobamate. The corresponding frequency of these events is shown in [Figure 50](#).

Figure 49 Study C021, Median Study Day of TEAE by Preferred Terms , TEAE Frequency Group ≤1%, SAE and Discontinuation Excluded

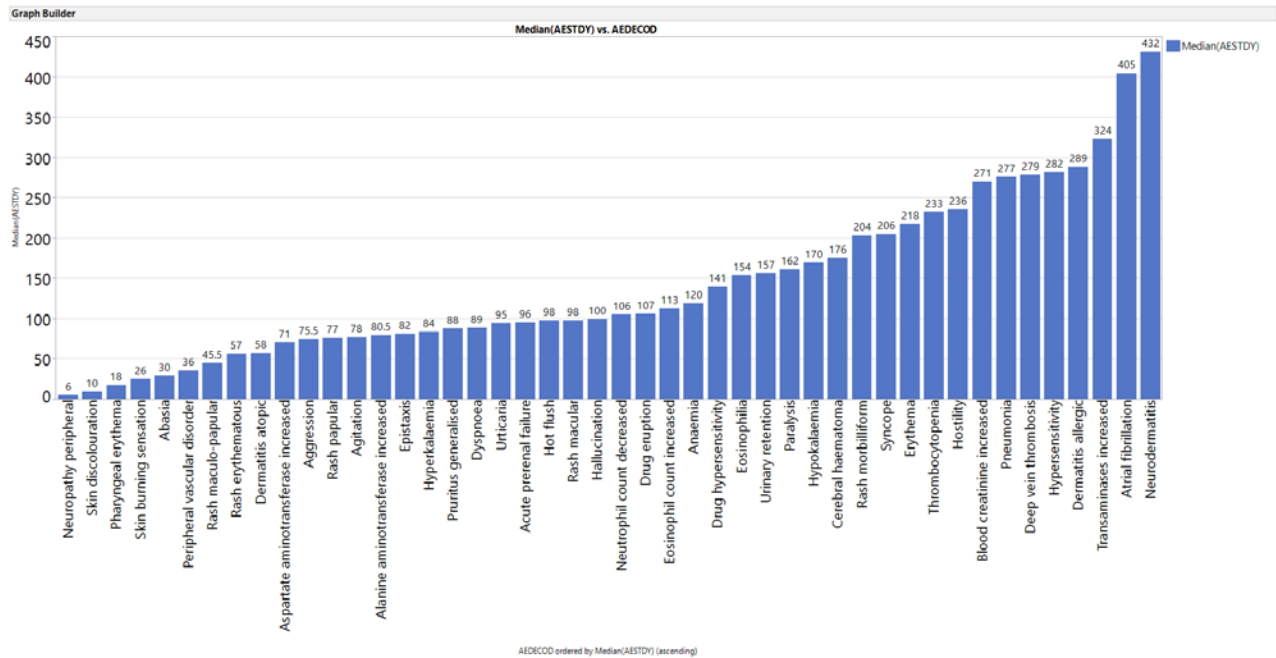
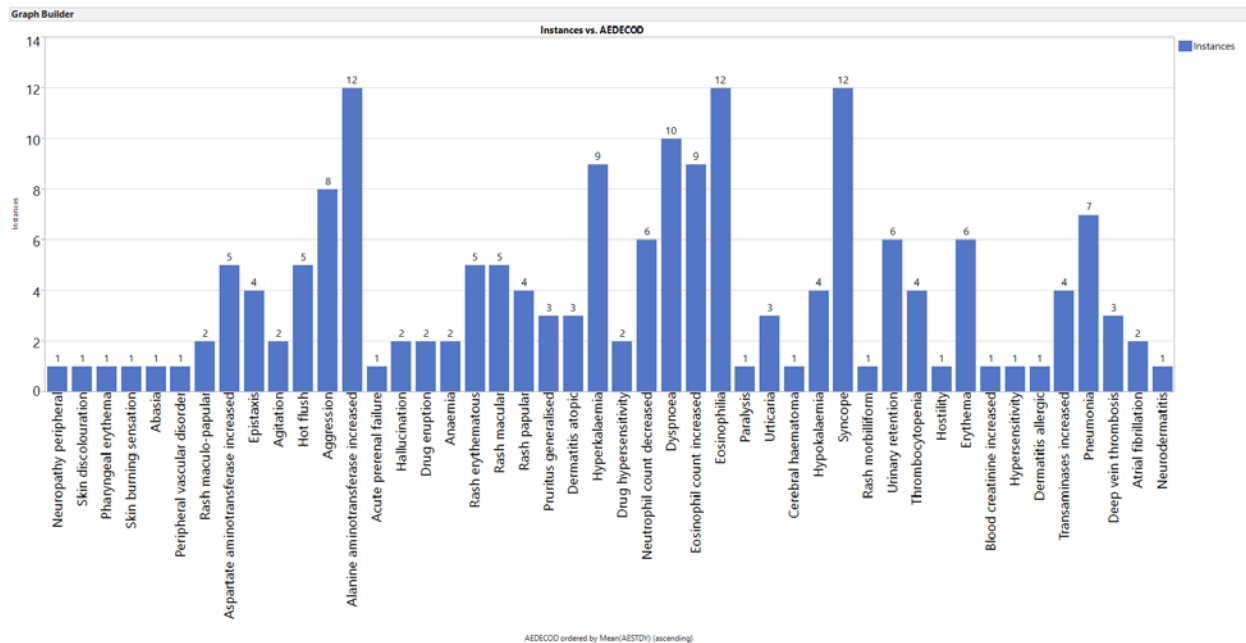


Figure 50 Study C021, Instances of TEAE by Preferred Terms , TEAE Frequency Group ≤1%, SAE and Discontinuation Excluded



Reviewer Comment, C021 TEAE:

Study C021 has the greatest number of patient years of exposure but not the longest duration of exposure, this is due to a larger patient population in study C021. Longest duration is captured in the open label extensions of Studies C013 and C021. The spectrum of TEAEs seen in this open label exposure are very similar to those seen in the C013-C017 open label extension.

The highest frequency events, seen in >10% of patients, were related to CNS dysfunction, the preferred terms include “somnolence”, “dizziness”, and “fatigue”. Headache, a fourth term with an occurrence >10% is not a CNS dysfunction term. The basis for “headache” is uncertain. Additional frequent events include “Viral upper respiratory tract infection”, “Nausea”, “Upper respiratory tract infection”, “diplopia”, “balance disorder”, “constipation”, “vision blurred”, “diarrhoea”, and “fall” at frequencies of 8%, 7%, 7%, 6%, 6%, 4%, 4%, 4%, and 4% respectively. Again, the majority of these terms are related to CNS dysfunction. The events of “Viral upper respiratory tract infection”, “Nausea”, “Upper respiratory tract infection”, are not unexpected events due to a high background rate. “Constipation” occurs at approximately the same rate as “diarrhoea” thus it is possible these events are influenced by background rate. “nausea”, “vomiting” and “diarrhoea” were judged generally as “mild” or “moderate” intensity, therefore do not appear to represent a safety threat.

“Pneumonia” occurs in 10 patients where 5 have an entry as an SAE. Judgement on the causality and safety threat of this event is difficult due to a high background rate of pneumonia. The events did not have a consistent temporal relationship to start of cenobamate treatment and in 7 of 10 cases were judged as “mild” or “moderate” severity. This event does not rise to threshold for entry into labeling.

Low frequencies of electrolyte abnormalities occur including hypokalemia and hyponatremia, but these are likely sporadic background events. There are 4 events of deep vein thrombosis”, in one case related to a severe cardiac event but otherwise appear sporadic and not coupled to cenobamate treatment.

The low frequency but highly serious cardiac adverse events are captured in the discussion of “serious adverse events” and “discontinuations”

Hypersensitivity events of rash, dermatitis, drug eruption, and “eosinophil count increased” are consistent with the hypersensitivity signal that has been identified in association with cenobamate treatment.

8.4.7. Laboratory Findings

C013

Means

Mean change from baseline at study visits 4, 6, 8, 10 and 12 are examined for departure from baseline value. Where outliers are identified in the box plots, the individual patient trends of departure from baseline are examined. Overall change from baseline and percent change from baseline were also examined for glucose, RDW, Hemoglobin, and Neutrophils.

Table 47 Study C013 DB, Group Mean Change from Baseline, Select Laboratory Values by Study Visit & Treatment Arm

		PBO						YKP					
		V4	V6	V8	V10	V12	Summary Mean V4-V12	V4	V6	V8	V10	V12	Summary Mean V4-V12
1	EOS	0.01	-0.01	-0.01	-0.01	-0.01	0.00	0.02	0.01	0.01	0.01	-0.01	0.01
1	HGB	0.07	-0.20	-0.16	-1.43	-1.01	-0.55	-0.38	-1.16	-1.87	-2.26	-1.97	-1.53
1	LYM	-0.03	-0.04	-0.07	-0.14	-0.10	-0.07	0.04	0.02	-0.04	-0.14	-0.08	-0.04
1	MONO	0.00	0.00	0.01	-0.02	-0.02	-0.01	0.02	0.02	0.01	0.01	-0.02	0.01
1	NEUT	-0.03	0.13	0.24	0.20	0.03	0.12	-0.17	-0.11	-0.24	-0.32	-0.43	-0.26
1	PLAT	3.38	2.61	6.94	1.87	2.76	3.51	0.87	-1.96	-4.96	-5.66	-12.21	-4.78
1	RDW	0.03	0.14	0.04	0.04	0.12	0.07	0.08	0.21	0.36	0.52	0.66	0.37
1	WBC	-0.06	0.08	0.18	0.05	-0.11	0.03	-0.10	-0.08	-0.26	-0.44	-0.55	-0.27
2	ALB	-0.09	-0.03	0.06	-0.34	-0.35	-0.15	-0.40	-0.37	-0.31	-0.78	-0.29	-0.43
2	ALP	-0.54	-0.32	0.40	-0.87	-0.70	-0.41	-0.05	0.14	0.99	1.00	2.68	2.40
2	ALT	-0.60	-0.37	0.40	-1.28	-0.17	-0.40	0.35	0.94	1.13	0.33	0.17	0.58
2	AST	-0.09	0.76	0.67	0.35	-0.08	0.32	-0.55	0.04	0.43	0.11	0.08	0.02
2	BILI	0.24	0.19	0.23	0.02	-0.18	0.10	-0.65	-0.98	-1.20	-1.68	-1.37	-1.17
2	BUN	0.08	0.09	0.14	-0.02	0.05	0.07	-0.09	0.04	0.00	0.22	0.45	0.12
2	CA	-0.01	-0.01	0.00	-0.02	-0.02	-0.01	-0.01	-0.02	-0.02	-0.03	-0.01	-0.02
2	CL	0.17	0.56	0.37	-0.28	0.50	0.26	0.05	-0.19	0.00	-0.26	-0.21	-0.12
2	CREAT	-0.03	0.66	0.54	-0.38	-0.46	0.07	0.03	0.32	-1.06	-0.07	0.72	-0.01
2	GLUC	0.00	-0.01	0.02	-0.01	-0.08	-0.02	0.15	0.05	0.11	-0.09	-0.05	0.02
2	K ⁺	-0.01	-0.07	-0.01	0.00	-0.05	-0.03	0.07	0.10	0.12	0.12	0.14	0.11
2	Na ⁺	-0.54	-0.08	0.10	-0.48	-0.02	-0.21	-0.09	-0.08	0.25	0.01	0.04	0.03
2	PHOS	0.00	0.00	0.00	0.00	-0.01	0.00	0.01	-0.02	0.01	0.00	0.04	0.01

	Comments Corresponding to Table 47
	YKP comment
ALT	
AST	
ALB	
ALP	
BILI	
BUN	
CA	
CL	sporadic V10 decline outlier- sporadic
CREAT	High change outliers @ V10 are sporadic
GLUC	large decline outlier at V10 and 12 examined { YKP3089C013-404004), hypoglycemia at baseline 250mg/dl, decline to 120mg/dl at V10. No decline below normal. Waterfall min values, no difference except pt 404004
PHOS	
K	Small positive mean change over PBO. YKP3089C013- (b) (6) (max 5.7 meq/L from inc 1.7- sporadic high), YKP3089C013- (b) (6) (meq 4.9 meq/L, chg + 1.5 V4, 1.4 V6)high outliers V4, V6. Low change outlier- YKP3089C013- (b) (6), -1.1 and -1.4meq/L at V4 and V6. None OORR low.
SODIUM	five patients examine with max negative change. Two had values that dropped to OORR low. Four were sporadic, one had sustained decline of 3 to 4 meq/L but none OORR low. Max increase over baseline, 5 examined- in case 1 sporadic increase, case 2 sustained increase over baseline @ 5meq, 8meq/L, 5meq/l, 6meq/l over baseline, 1 OORR high. , case 3 sporadic with an OORR high value, case 4 had low RR baseline with max increase of 5meq/L, no OORR, case 5 low RR baseline with max increase 9meq/L to 143 meq/L, no OORR
EOS	4 cases, max outliers identified in box plots. All sporadic and inconsistent elevations
RDW	YKP3089C013- (b) (6) OORR high baseline, high outlier at V6, V8 , V10, ADAE of microcytic-hypochromic anemia, no SAE entered at screening. YKP3089C013- (b) (6) normal at baseline with sustained rising trend-
HGB	
WBC	1 OORR low
LYM	
MONO	
NEUT	1 OORR low, UTI on ADAE
PLAT	

Means

Table 48 C013 Group Mean for Select Laboratory Parameter by Visit Day and Treatment Arm

Lab Parameter	PBO								YKP							
	V1	V3	V4	V6	V8	V10	V12	SUM mean	V1	V3	V4	V6	V8	V10	V12	SUM mean
Alanine Aminotransferase	20.7	21.2	20.4	21.3	22	19.5	21.8	21.0	19.1	19.3	20.2	20.5	20.7	20.1	19.5	20.1
Albumin	46.6	45.9	45.8	45.8	45.9	45.4	45.5	45.7	46.4	45.7	45.3	45.3	45.4	45	45.4	45.4
Alkaline Phosphatase	79.5	79.2	78.3	78.2	78.5	77.3	77.6	78.2	76.5	73.5	73.9	73.1	73.3	74.5	74.7	73.8
Aspartate Aminotransferase	20.8	20.4	20.2	21.1	21.1	20.1	20.4	20.6	20.1	20	19.8	20.2	20.5	20.4	20	20.2
Basophils	0	0	0	0	0	0	0	0.0	0	0	0	0	0	0	0	0.0
Bilirubin	5.8	5.7	5.9	6	5.9	5.7	5.6	5.8	5.9	6.1	5.5	5.2	5	4.5	4.6	5.2
Blood Urea Nitrogen	4.3	4.2	4.3	4.3	4.3	4.2	4.2	4.3	4.3	4.1	4	4.1	4.1	4.3	4.6	4.2
Calcium	2.4	2.4	2.3	2.3	2.3	2.3	2.3	2.3	2.4	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Chloride	103	102	103	103	103	102	103	103	104	103	103	103	103	103	103	103
Creatinine	74.6	73.6	73.6	74.3	74.2	73.6	73.4	73.8	71.8	71.9	72.2	72.6	71.1	72.5	73	72.2
Eosinophils	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Erythrocytes	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.3	4.3	4.4
Erythrocytes Distribution Width	13.9	13.8	13.9	13.9	13.9	13.8	13.9	13.9	14.4	14.3	14.3	14.5	14.7	14.8	15	14.6
Glucose mmol/L	5	5	5	5	5	5	4.9	5.0	5.1	5.1	5.3	5.2	5.2	5	5.1	5.2
Glucose mg/dl	90.1	90.1	90.1	90.1	90.1	90.1	88.2	89.7	91.9	91.9	95.5	93.7	93.7	90.1	91.9	92.8
Hb g/dL	14.1	13.9	13.9	13.9	13.9	13.8	13.9	13.9	13.6	13.5	13.6	13.5	13.4	13.4	13.4	13.4
Leukocytes	6.3	6.3	6.1	6.3	6.4	6.2	6.1	6.2	6.5	6.2	6.1	6	5.9	5.7	5.7	5.9
Lymphocytes	2	2	2	2	2	1.9	2	2.0	2	1.9	2	2	1.9	1.8	1.9	1.9
Monocytes	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Neutrophils	3.8	3.6	3.5	3.7	3.8	3.8	3.6	3.7	3.9	3.7	3.5	3.5	3.4	3.3	3.3	3.5
Phosphate	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.2	1.1	1.2	1.1	1.2	1.1	1.2	1.2
Platelets	226	226	228	224	228	222	223	225	232	230	227	225	221	221	218	224
Potassium	4.4	4.4	4.3	4.3	4.4	4.4	4.3	4.4	4.3	4.3	4.3	4.4	4.4	4.4	4.4	4.4
Sodium	141	141	140	141	141	140	141	141	141	141	141	141	141	141	141	141

Reviewer Comment: Analysis of the mean change from baseline and group mean value by study visit for select laboratory parameters was performed. The mean changes from baseline reveal a small mean increase in alkaline phosphatase at all visit that is reflected in the summary mean of the cenobamate treatment arm. There is no clear mechanism seen during the analysis of adverse events. Examination for OORR high values, next section, does not reveal a notable difference in distribution from placebo. Chloride reveals a decline from baseline compared to placebo at visits 6 and 12. There is also a decline in the overall mean for all visits in cenobamate treatment compared to placebo. Glucose had a positive change from baseline at visits 4, 6, and 8 in the cenobamate treatment arm compared to placebo. Examination of the group mean values by visit also reveals a small increase over placebo at all but visit 7. There is a consistent trend of positive mean change from baseline for potassium at all visits compared to placebo. The frequency of OORR high values for potassium is examined in the next section (outlier values). Examination of serum sodium reveals a small positive change from baseline in the cenobamate treatment arm not present in the placebo arm at visits 8, 10 and 12. Examination of the Erythrocyte Distribution Width (RDW) mean change from baseline reveals the cenobamate treatment arm has a positive value at all visits and an increase over the placebo change from baseline at all visits. The distribution of RDW values and OORR high outliers is presented in the next section. There is a negative change from baseline in the cenobamate treatment arm for hemoglobin values at all study visits that is larger than seen in the placebo arm. There is also a negative change in group mean values from baseline at all study visits for leukocyte measurements. This is also greater than the change from baseline for placebo at corresponding visit. This is explored further in the next section. Like leukocytes the neutrophil values had a negative group mean change from baseline at all study visits post baseline, also greater in magnitude than any values in the placebo arm. This same trend is seen in for platelets.

In summary, there is a mild myelosuppressive effect seen in the cenobamate treatment arm compared to placebo. The mean changes from baseline are not of large magnitude but suggest a possible consistent systematic effect and raises the question whether this change is related to the shift to a higher RDW value in the cenobamate treatment arm. This will be explored further in the examination of hematologic outliers in the next section. There is a small change toward increase in sodium and potassium values.

Outliers-High Values

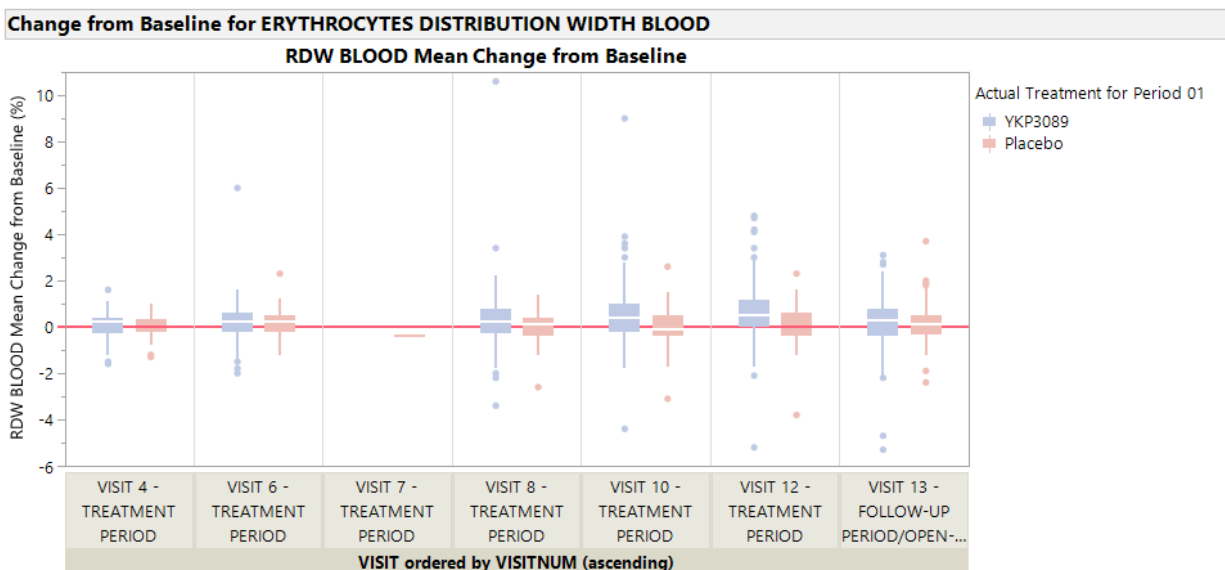
Laboratory values for core parameters where increase from baseline may signal a pathologic process are examined using JMP Clinical Waterfall Plots. These Parameters are shown in [Table 49](#). This analysis of maximum value normalized to ULN did not identify evidence of notable hematology or clinical chemistry outliers.

Table 49 Study C013, Select Laboratory Parameters Examined for Maximum Value (outlier values) at Any Measurement, Normalized to ULN, OORR High (excluding post treatment follow up visit)

Laboratory Parameter	Findings, cenobamate treatment	comment												
Alkaline Phosphatase	Max 1 x ULN	PBO-YKP, similar profile												
Alanine Aminotransferase	None > 1.7 x ULN	PBO-YKP, similar profile												
Aspartate Aminotransferase	Max 1.8 x ULN , one patient	PBO-YKP, similar profile												
Bilirubin	None > ULN	PBO-YKP, similar profile												
Blood Urea Nitrogen	Max 1.2 x ULN , one patient	PBO-YKP, similar profile												
Calcium	None > ULN	PBO-YKP, similar profile												
Chloride	None > ULN	PBO-YKP, similar profile												
Creatinine	None > ULN	PBO-YKP, similar profile												
Eosinophils (10 ⁹ /L)	4 patients > 2 x ULN, 1 AE "eosinophilia". No Hypersensitivity relate AE.													
Glucose	12 patients in the cenobamate arm have an increase in glucose > 36 mg/dl compared to 10 in the PBO arm	PBO-YKP, similar profile, no meaningful difference in frequency of high outliers between treatment arms.												
Potassium	Max 1.2 x ULN, one patient. Change from Baseline analysis increase >1meq/L reveals 3 patients in PBO and 6 in cenobamate <table border="1" data-bbox="586 1066 1114 1188"> <thead> <tr> <th>TRT01A (shift from baseline)</th> <th>N Rows</th> <th># Patients</th> <th>% Patients</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td>109</td> <td>8</td> <td>7.3</td> </tr> <tr> <td>YKP3089</td> <td>113</td> <td>19</td> <td>16.8</td> </tr> </tbody> </table>	TRT01A (shift from baseline)	N Rows	# Patients	% Patients	Placebo	109	8	7.3	YKP3089	113	19	16.8	PBO-YKP, similar profile, small trend toward increase K change from baseline in cenobamate
TRT01A (shift from baseline)	N Rows	# Patients	% Patients											
Placebo	109	8	7.3											
YKP3089	113	19	16.8											
Lymphocytes (10 ⁹ /L)	1 patient, maximum 1.3 x ULN	PBO-YKP, similar profile												
Neutrophils (10 ⁹ /L)	2 > ULN, Max 1.2 x ULN	PBO-YKP, similar profile												
Neutrophils Band Form (10 ⁹ /L)	None entered													
Platelets (10 ⁹ /L)	2 patients > 1.2 x ULN, 1 at 1.16 x ULN, second at 1.2 x ULN, patient has high minimum	PBO-YKP, similar profile												
Leukocytes (10 ⁹ /L) WBC	1 patient at maximum 1.2 x ULN	PBO-YKP, similar profile												
Method: JMP Clinical Waterfall Plots, examine for values >ULN on Observed Result Plot, excluding baseline and post treatment follow up visits														

Erythrocyte Distribution Width (RDW): there is a positive group mean increase value for RDW in the cenobamate treatment arm at all post baseline visits. In the placebo arm there is a smaller positive change.

Figure 51 C013 DB, RDW Box Plot of Study Visits, Change from Baseline, Group Mean and Median values



Outliers, Low Values post baseline (from JMP Clinical waterfall plots)

Table 50 Outliers, Low Values post baseline (from JMP Clinical waterfall plots)

Laboratory Parameter	Findings, cenobamate treatment	comment
Calcium (mmol/L) (CA)	Min .88 x LLN, one patient,	Sporadic low value, study day 36 (YKP3089C013- (b) (6) PBO-YKP, similar profile
Chloride (mmol/L) (CL)	Min 0.95 x LLN	PBO-YKP, similar profile
Glomerular Filtration Rate (mL/min/1.73m2)	No entries	
Glucose	Min, 0.76 x LLN,	No entries in ADAE dataset, sporadic. PBO-YKP, similar profile
Glucose < 70mg/dL		
Treatment arm # patients % patients		
Placebo 10 9		
YKP3089 10 9		
Hemoglobin	Min, 0.5 x LLN	Baseline value, all subsequent values higher although remain below LLN (YKP3089C013- (b) (6) Pt has ADAE entries for hyponatremia and hypochloremia. Overall- PBO-YKP, similar profile
Potassium	Min, 0.943 x LLN	PBO-YKP, similar profile
Lymphocytes (10 ⁹ /L)	Min, 0.96 x LLN	PBO-YKP, similar profile
Neutrophils (10 ⁹ /L)	2 patients <0.5 LLN (critical value),	AE profile of 2 critical OORR low patients examined. Patient YKP3089C013- (b) (6) has viral syndrome entry day -36 pre-treatment. Otherwise neither patient has infection entry. PBO-YKP, similar profile

Laboratory Parameter	Findings, cenobamate treatment	comment
Platelets (10 ⁹ /L)	Min, .46 x LLN, near critical study day 85	All values for Min patient (YKP3089C013- (b) (6)) are OORR low from baseline. Minimum value is sporadic among low values.
Sodium	Min, 0.96 x LLN	PBO-YKP, similar profile
Leukocytes (10 ⁹ /L)	Min, 2 patients 0.66 x LLN.	Patient YKP3089C013- (b) (6) OORR Low at baseline with intermittent OORR low values during study. Patient YKP3089C013- (b) (6) low in RR at baseline with sporadic OORR low on study day 37, PBO-YKP, similar profile

Shift Plot, Select Hematology

Method, JMP clinical Shift Plot, normal baseline to values normalized to either ULN or LLN for maximum or minimum post baseline value across all treatment visits.

Hemoglobin

There were no shifts of hemoglobin from reference range at baseline to OORR high post baseline.

There were 12 cenobamate treated patients and 10 placebo patients with a shift from normal baseline hemoglobin value to a minimum (peak absolute value) from any visit that is OORR low.

Neutrophils

There were 6 patients in the placebo arm and 3 in the cenobamate treatment arm with a shift from normal baseline to OORR high at the post baseline maximum value for all visits.

There were 18 patients in the cenobamate treatment arm and 16 patients in the placebo arm where the post baseline minimum was OORR low. The maximum low was .65 x 10⁹/L observed in a cenobamate treatment patient while the maximum magnitude of shift was from 6.22 x 10⁹/L at baseline to 1.19 x 10⁹/L during treatment. Both patients were in the cenobamate treatment arm.

Platelets

There were no placebo patients with a shift to from normal baseline to OORR high post baseline while there was one cenobamate treatment patient with a shift from 1.009 x ULN at baseline to 1.22 x ULN at maximum post baseline value.

There were 6 patients in the cenobamate treatment arm and 7 patients in the placebo treatment arm with a maximum decline post baseline to OORR low. The maximum shift and lowest value occurred in the placebo treatment arm.

Leukocytes

There were two each placebo arm and cenobamate treatment arm patients where the post baseline maximum value was a shift from normal to OORR high. The maximum increase was seen in a cenobamate treatment patient with an upshift of 5.9×10^9 /L.

There were 20 patients in the cenobamate treatment arm and 15 in the placebo arm with a minimum (maximal decline) value that was a shift to OORR low at any post baseline visit. The mean decline of the 15 placebo patients was -0.32 while the mean decline in the cenobamate patients was -0.41 with a median of -0.27 and -0.35 respectively.

Shift Plot , Select Chemistry

(method, JMP shift plot, minimum value shift baseline to treatment, normalized to LLN)

Sodium

Shift to Low

There are 5 cenobamate and 4 placebo patients with a shift from normal baseline to OORR low at any post baseline measurement. The minimum sodium value was 127meq/L from a baseline of 137meq/L. Mean sodium value from the 5 cenobamate treatment patients was 128.6meq/L.

Shift to High

Examination of the shift of maximum post baseline sodium values reveals an equal number of placebo and 200mg treatment arm patients had a shift from normal to OORR high. The maximum post baseline shift in the cenobamate treatment arm was to 149meq/L

Potassium

Shift to low

There are 2 placebo arm patients and 1 cenobamate patient with a shift from normal baseline to a maximum OORR low value at post baseline. The cenobamate patient shifted to a value of 3.29meq/l.

Shift to High

From baseline normal there were 4 cenobamate treated patients and 2 placebo arm patients with a shift to OORR high. The maximum cenobamate treatment patient shift was to 1.07 x ULN.

Glucose

Shift to High

From baseline normal the maximum post baseline glucose shifts are compared. This examination reveals 13 cenobamate patients and 11 placebo patients with a shift from with

reference range to OORR high. Visual inspection reveals the placebo group of 11 have a greater magnitude upshift than the cenobamate group.

Reviewer Comment, C013 Laboratory Summary:

Calculation of group mean change from baseline by study (Table 47) visit for the selected laboratory parameters reveals a small mean negative change from baseline for hemoglobin, neutrophils, platelets, leukocytes, and chloride. Where there is a similar change in the placebo arm the change in the cenobamate arm is larger. There is a small mean increase in the cenobamate treatment are seen for RDW, alkaline phosphatase, glucose, potassium and sodium.

Group mean values (Table 48) reflect the calculated group mean changes except for chloride and sodium where there was no difference at any visit for mean values.

Outlier values for the selected laboratory parameters are examined using JMP Clinical waterfall plots for both high and low outliers by observed result, greater than upper or lower limits of normal.

The examination for OORR high values reveals notable abnormalities for eosinophils where there were 4 patients with an entry $> 2 \times \text{ULN}$ in the cenobamate treatment arm. Examination of corresponding adverse event dataset did not identify any entries for hypersensitivity reactions among these patients. Analysis of potassium values revealed 1 patient with a post baseline entry of $1.2 \times \text{ULN}$. A subsequent change from baseline analysis revealed a $>1\text{meq/L}$ increase in 6 cenobamate treated patients and 3 placebo treated patients. Examination of glucose revealed 12 patients in the cenobamate treatment arm with a $>36\text{meq/L}$ increase and 10 patients in the placebo arm with an increase of the same magnitude.

The low value examination reveals generally sporadic OORR low outliers. There were notable neutrophil outliers where 2 patients had entries for critical values that were less than $500 \times 10^9/\text{L}$. These were seen in 2 patients. Examination of the adverse event profile reveals that one of these patients has a viral infection during baseline that may account for the neutropenia. The second patient had no confounding event but was a sporadic value rather than part of a sequential trend. Neither patient had a post baseline infection. There was a single patient with a platelet value that decline to $64 \times 10^9/\text{L}$. This value was a sporadic lowering of a profile of values that were all OORR low at all entries including baseline. Leukocyte evaluation revealed two patients with values of $2.7 \times 10^9/\text{L}$. One of these patients had a low baseline value while the second had a low normal value at baseline with a single sporadic OORR low on study day 37.

Shift examinations were performed on select hematology and chemistry parameters including hemoglobin, leukocytes, neutrophils, platelets, sodium, potassium, and glucose.

The shift examinations revealed no substantive frequency or magnitude of change among the minimum or maximum, high or low values that were OORR during the post baseline treatment

interval for the selected chemistry parameters. The shift examination also no substantive frequency or magnitude of change among the minimum or maximum, high or low values that were OORR during the post baseline treatment interval for the selected hematology parameters.

Overall examination of the study C013 safety laboratory dataset reveals small mean positive or negative change from baseline across study visits that did not translate into substantive frequency of treatment related outliers or shifts from normal at baseline.

C017

Hematology

Table 51 Hematology , Group Mean Values by Treatment Arm and Study Visit

H /C	LBTEST	PBO				100mg				200mg				400mg			
		V3	V6	V9	mean	V3	V6	V9	Sum	V3 Base	V6	V9	Sum	V3 Base	V6	V9	Sum
1	Basophils	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	Eosinophils	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1	Erythrocytes	4.6	4.6	4.5	4.6	4.6	4.5	4.5	4.5	4.5	4.4	4.4	4.4	4.5	4.4	4.4	4.4
1	Erythrocytes Distribution Width	14.6	14.5	14.4	14.5	14.5	14.6	14.5	14.5	14.4	14.8	14.5	14.6	14.4	15	14.9	14.8
1	Hemoglobin	138.6	136.9	136.6	137.4	140.5	139.6	138.3	139.5	139.8	137.5	138.2	138.5	138.7	133.8	136.1	136.2
1	Leukocytes	6.3	6.5	6.4	6.4	6.4	6.2	6.3	6.3	6.7	6.3	6	6.3	6.2	5.7	5.7	5.9
1	Lymphocytes	1.9	2	1.9	1.9	1.9	1.9	1.9	1.9	2	2	1.9	2	2	1.8	1.8	1.9
1	Monocytes	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
1	Neutrophils	3.8	3.9	3.9	3.9	3.9	3.7	3.8	3.8	4.1	3.7	3.5	3.8	3.7	3.3	3.4	3.5
1	Platelets	236.4	241.8	239.7	239.3	233.8	228.7	226.9	229.8	236.3	229.8	227.9	231.3	238	233.3	234.3	235.2

Eosinophils: examination of post baseline eosinophil values for OORR high reveal 2 patients, one each in the 200mg and 400mg arm were OORR high at baseline and remained high. There is no substantive difference between placebo and treatment group mean percent change from baseline (method: mean value of visit 3 and Visit 9 compared to value at visit 3)

Erythrocytes Distribution Width: There were 6 patients with OORR high outlier values of >20 while the ULN is 14.5%. There were no values over 20% in the PBO arm. All of these patients had high baseline values. The adverse event dataset for these patients was examined and no entries from the “blood and lymphatic disorders” SOC were present. There a small increase in group mean values over baseline.

Reviewer Comment: There is no clinically identifiable impact of the post baseline positive change in RDW.

Hemoglobin: There is no notable group mean change from baseline visit or from placebo. Post baseline values were examined. There were 3 (3%), 1 (1%), 4 (3.6%), and 7 (6%) patients in the placebo, 100mg, 200mg and 400mg treatment arms with a decline from baseline >1.5g/dL hemoglobin. Examination of the patient cohort with normal baseline hemoglobin values revealed that 1.9%, 6.5%, 2.7% and 2.7% in the placebo, 100mg, 200mg and 400mg treatment arm had OORR low post baseline hemoglobin values.

Reviewer Comment: Based on the low frequency of OORR low values, sustained sequential decline and sporadic occurrence and small separation from placebo in the high dose treatment arms, there is no clinically substantive change in hemoglobin values related to cenobamate treatment are identified.

Leukocytes:

Examination of group mean leukocyte values by visit and treatment arm reveal a small decline in group mean values that has a duration and dose relationship in the 200mg and 400mg treatment arms. Examination for low outliers among patients with normal baseline reveals there was an increase frequency of patients with post baseline OORR low values, compared to placebo, in the 200mg and 400mg treatment arms. The highest frequency was in the 400mg arm. There was no dose related decline in leukocyte count among the patients with OORR low post baseline values, see [Table 52](#). The percent change from baseline was examined. The overall trend of post baseline leukocyte values was assessed by examination of the proportion of patients that had a negative change compared to those with a positive change from baseline by treatment arm. There were a higher proportion of cenobamate treated patients with a negative percent change from baseline compared to the placebo treatment arm. This trend was also dose related where 39% of patients in the placebo arm, 53% of patients in the 200mg arm and 68% of patients in the 400mg cenobamate arm had a negative change in leukocyte value from baseline to double blind treatment interval, see [Table 53](#). Among those patients with OORR low values one was observed with a value <3.0 x 10⁹/L. This patient had a value of 2.7 x 10⁹/L.

Reviewer Comment: there was a trend to post baseline decline in leukocyte count that had partial relationship to dose. Examination of the magnitude of the decline did not identify a trajectory to critically low values and in most cases the declines were not part of a sequential decline of leukocyte count. Labeling should reflect that a dose related frequency of low leukocyte counts was seen. This may be placed in laboratory abnormalities subsection of section 6.

Table 52 C017, WBC Post Baseline OORR Low Values Where Baseline was Normal.

WBC: Any Post Baseline OORR low with normal Baseline				
Arm	# Pts	%Pts	Mean WBC	Median WBC
Placebo	4	3.7	3.3	3.25
100mg	4	3.7	3.2	3.1
200mg	7	6.4	3.3	3.5
400mg	11	9.9	3.3	3.4

Table 53 C017, Leukocytes- Change from Baseline, Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9) Compared to Baseline (Visit 3), Percent Change

Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9), % Change from Baseline Value (Visit 3)					
	Pt in Arm	Pts Positive % CHG	% Pts	Pts Negative % CHG	% Pts
Placebo	108	61	56	42	39
100mg	108	48	44	52	48
200mg	110	45	41	58	53
400mg	111	31	28	75	68

Lymphocytes: Examination of group mean lymphocyte values reveals a small decline in value in the 400mg treatment arm compared to placebo and the lower dose cenobamate treatment arms. Analysis of low post baseline values reveals notable trend in frequency of OORR low lymphocyte counts. The percent of patients within reference range at baseline that had OORR low values post baseline were 1.9%, 0%, 2.7%, 2.7% in the placebo, 100mg, 200mg, and 400mg treatment arms respectively, see [Table 54](#). Examination of all change from baseline revealed an increased proportion of patients with a negative change from baseline in the cenobamate treatment arms compared to placebo that was greatest in the 400mg group, [Table 55](#).

Reviewer Comment: There is a trend of decline in lymphocyte count associated with cenobamate treatment. This trend is small and does not reach a level of substantive clinical impact.

Table 54 C017, Lymphocytes, Frequency of OORR low Among Patients Within Reference Range at Baseline

Lymphocytes: Normal Baseline with OORR low Post Baseline value		
Actual Arm Code	# Patients	% patients
Placebo	2	1.9
100mg	0	0.0
200mg	3	2.7
400mg	3	2.7

Table 55 C017, Lymphocytes- Change from Baseline, Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9) Compared to Baseline (Visit 3), Percent Change

Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9), % Change from Baseline Value (Visit 3)					
Lymphocytes					
	Pt in Arm	Pts Positive % CHG	% Pts	Pts Negative % CHG	% Pts
Placebo	108	46	43	52	48
100mg	108	37	34	60	56
200mg	110	41	37	61	55
400mg	111	30	27	75	68

Neutrophils:

Examination of group mean neutrophil values by treatment arm and visit reveals a small decline in mean values in the 400mg arm compared to placebo and the lower dose cenobamate treatment arms. Examination of neutrophil values from among patients with a normal baseline value reveals there were 2.8%, 2.8%, 0.9% and 7.2% of patients in the placebo, 100mg, 200mg and 400mg treatment arm respectively with that were OORR low, [Table 56](#). A notable separation from placebo in the frequency of OORR low values occurs in the 400mg treatment arm. There were two values in the 400mg treatment arm and two in the placebo arm of $1.0 \times 10^9/L$, see [Figure 52](#). An examination of the proportion of patients that have a negative post baseline change in neutrophil count reveals that decline was in excess of an increase in the 200mg and 400mg treatment arm. This analysis also reveals that the magnitude of the decline was larger than placebo in all cenobamate treatment arms compared to placebo, [Table 57](#).

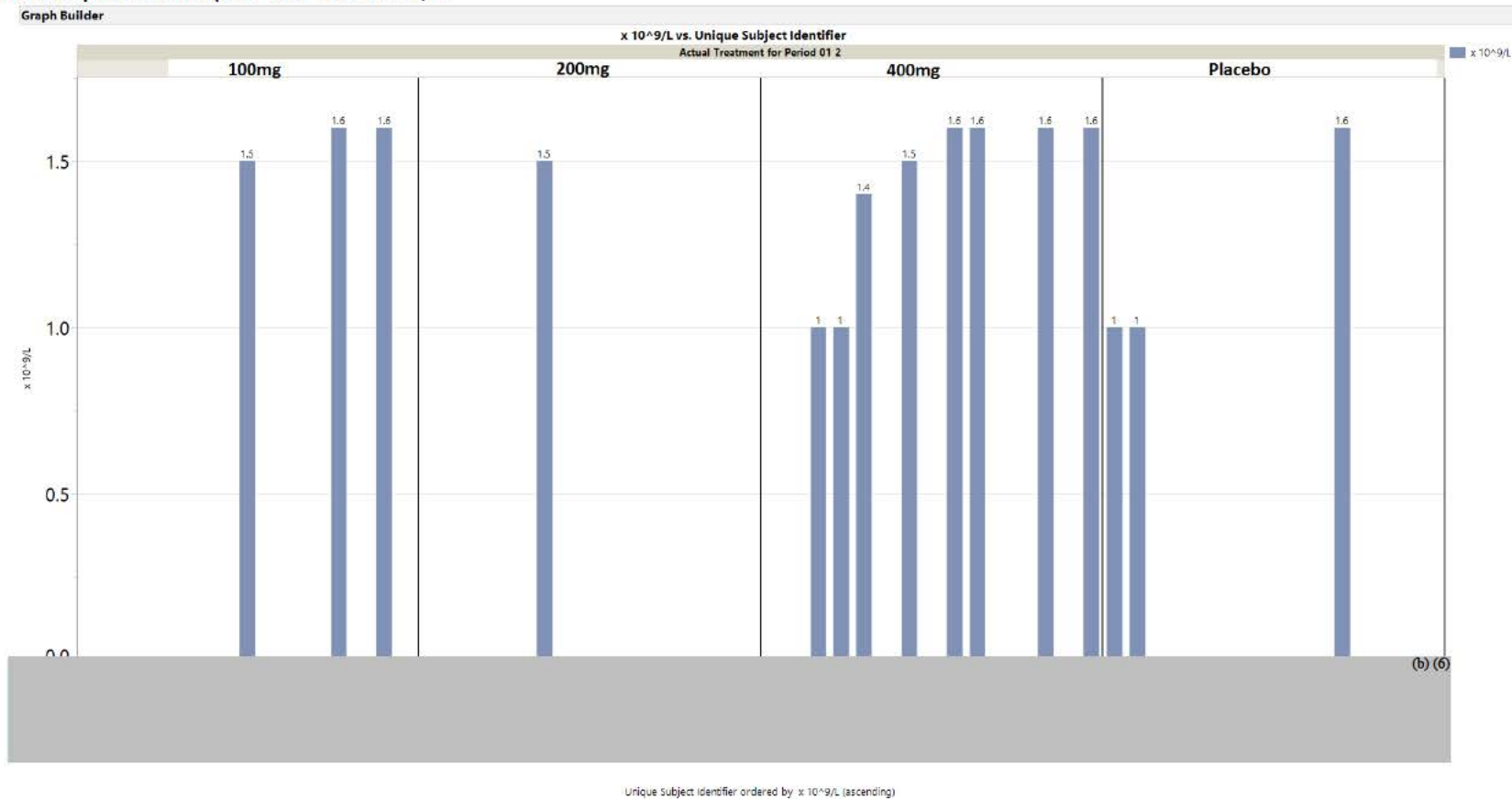
Table 56 C017, Neutrophils, Frequency of OORR low Among Patients Within Reference Range at Baseline

Any Post Baseline OORR low with normal Baseline		
Arm	# Patients	% Patients
Placebo	3	2.8
100mg	3	2.8
200mg	1	0.9
400mg	8	7.2

Table 57 C017, Neutrophils- Change from Baseline, Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9) Compared to Baseline (Visit 3), Percent Change

Mean Post Baseline Values (mean of WBC value @ Visit 6 & 9), % Change from Baseline Value (Visit 3)					
Neutrophils	Pt in Arm	Pts Positive % CHG	% Pts	Pts Negative % CHG	% Pts
Placebo	108	51	47	46	43
100mg	108	49	45	49	45
200mg	110	44	40	59	54
400mg	111	41	37	65	59

Figure 52 C017 Neutrophil Low Outlier, Any Post Baseline OORR low, Within Reference Range at Baseline, By Treatment Arm and Neutrophil Count (RR= 1.7-7.9 x 10⁹/L)



Reviewer Comment: There is a trend to lower neutrophil values that is dose related but the maximum (nadir) low OORR values in the cenobamate arm are not greater than the maximum (nadir) in the placebo arm. These analyses identify a property of cenobamate that lowers the neutrophil count, but the trend of these events does not have a trajectory to critically low values and the low outliers were generally sporadic rather than part of a sequential decline of neutrophil count. Labeling should reflect that a decline in neutrophil count is seen as an adverse effect in laboratory abnormalities.

Platelets: There was no decline in group mean platelet counts by treatment arm and study visit. Examination of post baseline OORR low platelet counts where baseline was normal reveals no notable change in frequency of low outliers by treatment arm. There were 3 OORR low post baseline values in the 400mg arm. Two of the three values were sporadic and the third was part of a sequential decline post baseline.

Table 58 C017, Platelets, Frequency of OORR low Among Patients Within Reference Range at Baseline

arm	# patients	% Patients	Comment: distribution of low values
Placebo	0	0.0	
100mg	1	0.9	Small decline trend from low RR
200mg	0	0.0	
400mg	3	2.7	sporadic day 42
			sequential decline
			sporadic day 129

Hematology Summary

Examination of the hematology parameters eosinophils, hemoglobin, erythrocyte distribution width, leukocytes, lymphocytes, neutrophils, and platelets reveals that a dose related decline in leukocytes to OORR low was present and there was an overall excess of post baseline decline in leukocyte count over an increase in leukocyte count. There was also a trend of decline in neutrophil count related to dose where the 400mg treatment arm had a notable separation from the frequency of OORR low post baseline values in the placebo treatment arm. There was also a higher frequency of post baseline declines in neutrophil count compared to post baseline increase in neutrophil count. The lowest values identified did not reach critical levels of $500 \times 10^9/L$. The lowest values identified were $1.0 \times 10^9/L$ with two occurrences each in the 400mg treatment arm and the placebo arm. There were no notable changes in the remaining parameters that were examined. Section 6 of labeling in “laboratory abnormalities” should reflect that a decline in leukocytes to OORR low during cenobamate treatment was observed that was dose related where 3.7%, 3.7%, 6.4% and 9.9% of the placebo, 100mg, 200mg, and

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Steven Dinsmore, DO
NDA 212839 (cenobamate) XCOPRI

400mg treatment arms respectively. The decline in neutrophils should also be included in the “laboratory abnormalities” in section 6 noting that the frequency of decline during cenobamate treatment to OORR low was 3% in the placebo arm and 8% in the 400mg arm.

Chemistry

Table 59 C017 Group Mean Values for Chemistry Parameters by Treatment Arm and Study Visit

H / C	LBTEST	PBO				100mg				200mg				400mg			
		V3	V6	V9	mean	V3	V6	V9	Sum	V3 Base	V6	V9	Sum	V3 Base	V6	V9	Sum
2	Alanine Aminotransferase	19	18	18	18	20	20	20	20	21	23	21	22	21	31	23	25
2	Albumin	46	46	46	46	46	46	46	46	47	46	46	46	46	45	45	46
2	Alkaline Phosphatase	76	76	77	76	77	79	80	79	74	79	83	78	77	79	83	80
2	Aspartate Aminotransferase	18	18	18	18	20	19	20	20	20	22	20	20	20	25	21	22
2	Bilirubin	5.5	5.4	5.6	5.5	5.4	4.6	4.6	4.9	5.7	4.6	4.7	5	5.4	4.4	4.5	4.8
2	Blood Urea Nitrogen	4.4	4.2	4.4	4.3	4.5	4.6	4.6	4.6	4.4	4.5	4.5	4.5	4.3	4.8	4.7	4.6
2	Calcium	2.4	2.4	2.4	2.4	2.4	2.4	2.3	2.4	2.4	2.3	2.3	2.3	2.4	2.3	2.3	2.3
2	Chloride	102	101	102	102	102	101	102	102	101	102	101	101	102	102	102	102
2	Creatinine	63	62	62	62	64	66	64	65	63	63	63	63	62	65	63	63
2	Glucose	5.13	5.33	5.11	5.2	5.15	5.15	5.11	5.1	5.18	5.4	5.38	5.3	5.26	5.24	5.21	5.2
2	Phosphate	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
2	Potassium	4.4	4.3	4.3	4.3	4.4	4.4	4.4	4.4	4.3	4.4	4.4	4.4	4.4	4.5	4.4	4.4
2	Protein	37.8	30	40.8	36.2	50		47.5	48.8	30		40	35	38.8		45.6	42.2
2	Sodium	140.3	139.6	140.2	140	140	139.8	140.4	140.1	140	140.2	139.3	139.8	140	139.8	140.1	140

ALT: Examination of group mean ALT values by study visit and treatment arm reveals a small increase over placebo that is dose related. There is no consistent trend by study visit. Examination of OORR high outlier values reveals 5 patients with post baseline elevations > 2 x ULN. Four of these patients had a value > 3 x ULN and one had a value >2 x ULN but < 3 x ULN. The patients that exceeded a value of 3 x ULN have their values and associated value trend expressed as narrative in the following paragraph:

YKP3089C017- (b) (6) : sporadic V6 YKP3089C017- (b) (6) : sporadic V9 YKP3089C017- (b) (6) : peak of 7.6 x ULN at V6 followed by steady decline to 2 x ULN at V10 with no significant elevation of bilirubin. YKP3089C017- (b) (6) : sporadic 3 x ULN V6, 1.4 X ULN @ V9. There was one additional patient with a post baseline value > 2 x ULN (with normal baseline). There were no other patients with values that exceeded 2 x ULN with normal baseline.

The mean value of both post baseline values is computed and compared to the baseline value. Examination of the distribution of the post baseline mean compared to the baseline reveals there was one post baseline mean that was in excess of 3 x ULN, this was patient YKP3089C017- (b) (6) whose post baseline mean was 4.63 x ULN. Analysis by this method revealed no mean of post baseline ALT values > 2.4 x ULN. There were 16 patients in the total of cenobamate treatment arms with a post baseline ALT value that was > 100% of baseline while there were none in the placebo treatment arm.

Reviewer Comment: there is an elevation of ALT associated with cenobamate treatment found in group means and by percent change from baseline analyses. The effect was dose related and reached a critical threshold of > 3 x ULN in one case. The overall trend does not show a trajectory to critical elevation and examination of high outliers reveals the excursion to high OORR was sporadic. These observations do not reach a threshold of clinical concern for drug induced liver injury but is captured as an adverse event in labeling of elevated AST in the adverse event category of investigations.

AST: Examination of group mean values by treatment arm and study visit reveals an elevation of AST that is in part dose related. Examination of outliers reveals 2 patients with a post baseline elevation of AST to > 3 x ULN. Both elevations are sporadic and not sustained in post baseline measurements.

Reviewer Conclusion: There is no signal for clinically substantive elevation of AST.

Calcium: examination of group mean calcium values across treatment arms reveals a small mean decline compared to baseline and placebo in the 200mg and 400mg treatment arms. Post treatment OORR High or Low calcium values were uncommon. There were 2 patients with small excursions to OORR low, one each in the 100mg and 200mg treatment arms. A systematic examination of post baseline OORR low values in patients with normal baseline reveals a small excess of OORR low values in the 400mg arm compared to placebo where three patients (2.7%) have OORR low values, [Table 60](#). These values are examined and reveal there is

a single OORR low occurrence in one patient “sporadic”. There are two post baseline low values in another patient that plateau and stop decline. There is a third patient with two post baseline OORR low values that reach a minimum then improve, a U-shaped curve, although not to within reference range.

Reviewer conclusion: the frequencies of departure from reference range calcium values during cenobamate treatment does not reach a threshold of a clinically substantive effect.

Table 60 C017, Calcium Values with Post Baseline OORR low in Patients with Normal Baseline

Calcium, Post Base OORR low, normal baseline			Distribution of OORR low values
arm	# pts	%Pts	
Placebo	2	1.9	
100mg	1	0.9	sporadic, last value
200mg	1	0.9	
400mg	3	2.7	2 post baseline, u shape
			2 OORR low post baseline, plateau
			1 sporadic post base, u shape

Chloride: There are no notable group mean changes detected in chloride values across treatment arms or study visits. Examination of post baseline chloride values among patients with a normal reference range value at baseline reveals a small excess of cases in the 200mg arm compared to placebo. There were 3.7%, 0.9%, 4.5% and 2.7% of patients in the placebo, 100mg, 200mg and 400mg treatment arms respectively with chloride values OORR low post baseline, [Table 61](#). The distribution of the OORR low values is also examined. in the 100mg arm there were two low values that did not progress sequentially but there was improvement, though not to normal range as the sequence progressed. In the 200mg arm there were 5 OORR low events captured in the examination of chloride value “nadirs” across the post baseline sampling. Four of these were single sporadic occurrences with in one case there were 2 OORR low that were progressively lower in sequence. In the 400mg arm there were three events where values for all study visits were evaluated. In these cases one was a single sporadic event, one patient had two OORR low values on their study timeline that had a maximum then improvement while still on therapy, a U shaped curve and the third patient had two OORR low events, also in a U shape curve, [Table 61](#).

Table 61 C017, Chloride Values with Post Baseline OORR Low Values in Patients with Normal Baseline.

Chloride			Distribution of OORR low values
Arm	# Pts	% Pts	
PBO	4	3.7	single day 41
			single, day 44
			sporadic day 50
			2 low sequential
100mg	1	0.9	2 low U shape
200mg	5	4.5	single day 126
			single day 72, U shaped
			single day 127 (88mmol/L)
			2 low sequential
			last value only
400mg	3	2.7	single day 126
			single, day 15 U shape
			2 low U shape

Reviewer Conclusion: there is no clinically substantive departure from normal chloride values associated with cenobamate treatment.

Potassium:

Examination of group mean change from baseline reveals a small increase from placebo to cenobamate treatment without a dose response. Capture of maximum (nadir) OORR low post baseline values from all dose groups and double-blind treatment period visits reveals the placebo arm had a higher frequency of OORR low potassium value than any cenobamate treatment arm, [Table 62](#). Analysis of the mean post baseline potassium values to identify patients with a post baseline trend of elevated potassium, reveals there were 2 (1.9%), 7 (6.5%), 7 (6.4%) , and 5 (4.5%) patients in the placebo, 100mg, 200mg and 400mg treatment arms that had a mean value OORR high respectively. The associated group mean and median potassium values in the treatment arms were 4% over ULN, there was no dose response, in this analysis of post baseline means, [Table 63](#). Capture of maximum (peak) OORR high post baseline values from all dose groups and double-blind treatment period visits identifies 37 patients where the maximum potassium value was OORR high. The highest post baseline maximum value of 5.9meq/L occurred in the 400mg treatment arm. The distribution of OORR high maximum values is as follows; 6 (5.6%), 9 (8.3%), 10 (9.1%) , and 12 (10.8%) patients in the placebo, 100mg 200mg and 400mg treatment arms respectively, [Table 64](#). The group mean elevation over ULN was 8% in all treatment arms. There was no dose response for mean potassium value but there was a dose response for frequency of OORR high, [Table 64](#). The profile of individual potassium values from those 37 patients with OORR high values are shown at visits 3,6, and 9, [Figure 53](#). This graphic covers 107 measurements from 37 post baseline OORR high patients. There are no excursions above the critical value of 6.0meq/L. There are 45 values > 5meq/L. In 26 of these instances the occurrence of OORR high potassium value is sporadic while in 11 instances there is a sequential increase from visit 3 to visit 9 with 2, 4 and 5 patients in the 100mg, 200mg and 400mg arm. The dose response in frequency of OORR high and maximum frequency of sequential potassium trend within individual patients from the 200mg and 400mg support a cenobamate treatment effect.

Table 62 C017, Potassium Values with Post Baseline OORR low in Patients with Normal Baseline

Potassium			Distribution of OORR low values
Arm	# Pts	% Pts	
Placebo	3	2.8	last value 3.4
			single day 42, U shape
			single day 41 U shape
100mg	0	0.0	
200mg	0	0.0	
400mg	1	0.9	single day 55, U shape

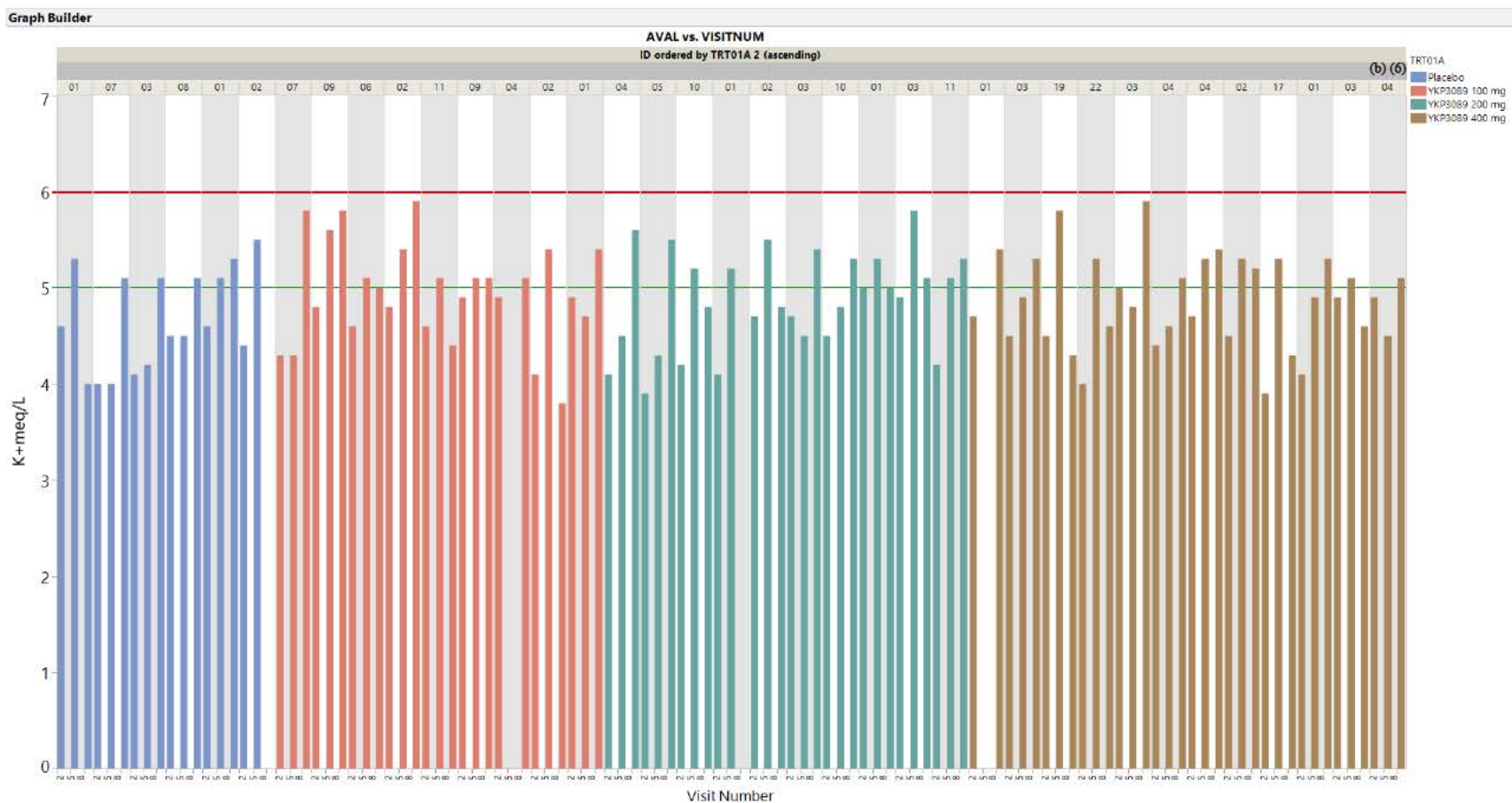
Table 63 C017 Mean of All Post-baseline Values Compared to Baseline in Patients Normal at Baseline with OORR mean High Post Baseline, Group Mean of Means and Median of Means.

Treatment Arm	# Pts	% Pts	Group Mean K+ (of Pts with Post Baseline OORR High mean)	Group Median K+ (of Pts with Post Baseline OORR High mean)
Placebo	2	1.9	5.4	5.35
YKP3089 100	7	6.5	5.2	5.1
YKP3089 200	7	6.4	5.2	5.15
YKP3089 400	5	4.5	5.2	5.2

Table 64 C017, Capture of Maximum Post Baseline Individual Value where Value is OORR High and Baseline Value Normal with Group Mean and Median K+ Value

Treatment Arm	# Pts	% Pts	Mean (K + Value)	Median (K + Value)	Max in group
Placebo	6	5.6	5.2	5.2	5.5
YKP3089 100	9	8.3	5.4	5.4	5.9
YKP3089 200	10	9.1	5.4	5.35	5.8
YKP3089 400	12	10.8	5.4	5.3	5.9

Figure 53 C017, K+, Patients (n=37), Post Baseline OORR High with Normal Baseline, Visits 3,6,9 by Treatment Arm and Potassium Value.



Reviewer Conclusion, K+:

Based on the frequency, dose response, and separation from placebo of increased serum potassium there is an association of elevation of serum potassium values with cenobamate treatment. The magnitude of the elevation in study C017 did not reach a CTCAE grade 3, however, the sponsor reports 2 patients in the C013-C017 OL extension pool had values in this range. The clinical meaning of the observations of potassium is uncertain. There is a higher baseline rate of OORR high than OORR low potassium. In the C017 laboratory dataset 27 (6.3%) patients had a baseline potassium value > 5.0meq/L while 2 (0.46%) had a baseline value <3.5meq/L. Although there was an excess of high baseline potassium values, the post baseline distribution of OORR high values was dose related with an excess frequency as cenobamate dose increased. The laboratory abnormalities subsection of section 6 should reflect that OORR high potassium values were in excess of placebo in a dose related distribution, occurring in 5.6%, 8.3%, 9.1% and 10.8% of the placebo, 100mg, 200mg, and 400mg treatment arms respectively, with a maximum value of 5.9meq/L.

Glucose: Examination of group mean glucose values across treatment arms and study visits does not reveal a consistent change. When the dataset is examined for a maximum value at any study visit that is OORR high from among patients with normal baseline values 6 patients are captured. There are 2 (1.9%) , 0 (0%), 3 (2.7%), and 1 (0.9%) from the placebo, 100mg, 200mg and 400mg treatment arms respectively, [Table 65](#). The mean post baseline glucose value is computed, and this mean value is compared to baseline to generate a percent change (mean) from baseline. The frequency of a positive percent change from baseline is greater than the frequency of a negative change from baseline in all treatment arms including placebo, [Table 66](#). When the frequency of positive percent change from baseline is examined there is only a small increase in treatment arm frequency over placebo positive change frequency.

Table 65 C017, Glucose Values with Post Baseline OORR low in Patients with Normal Baseline

Glucose, Capture Post Baseline Maximum value that is OORR high from cohort with normal baseline value		
	# Pts	% Pts
Placebo	2	1.9
100mg	0	0.0
200mg	3	2.7
400mg	1	0.9

Table 66 C017, Serum Glucose- Change from Baseline, Mean Post Baseline Values (mean of Glucose value @ Visit 6 & 9) Compared to Baseline (Visit 3), Percent Change

Mean Post Baseline Values (mean of glucose value @ Visit 6 & 9), % Change from Baseline Value (Visit 3)					
	Pt in Arm	Pts Positive % CHG	% Pts	Pts Negative % CHG	% Pts
Placebo	108	55	51	48	44
100mg	108	60	56	47	44
200mg	110	61	55	43	39
400mg	111	57	51	51	46

Table 67 C017, Any Post Baseline Glucose <70mg/dL by Treatment arm

treatment arm	# patients	% patients
Placebo	5	4.7
100mg	5	4.6
200mg	3	2.7
400mg	3	2.7

Reviewer Comment: Cenobamate treatment does not appear to be associated with increase in serum glucose values.

Sodium

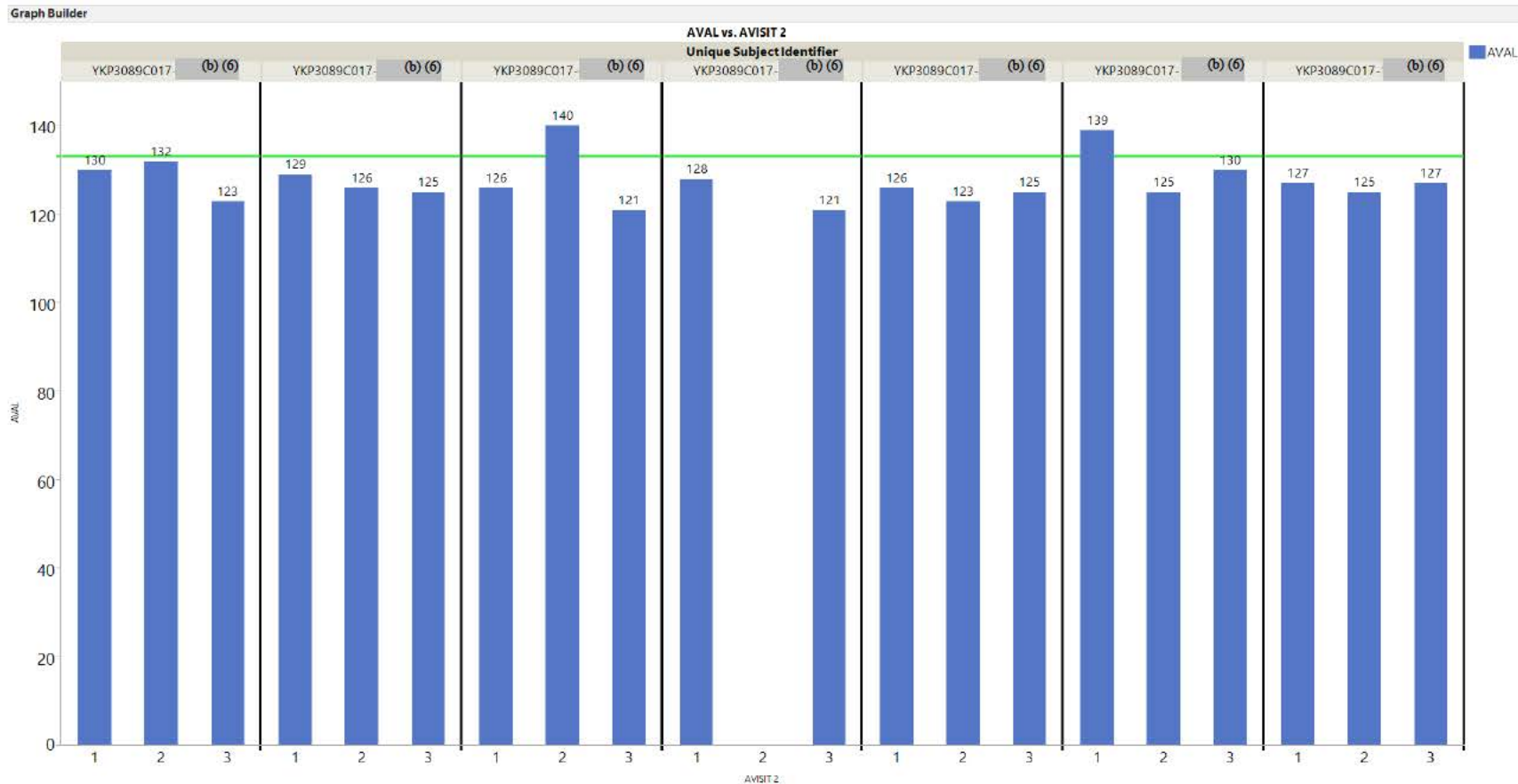
Examination of group mean values by study visit and across treatment arms does not reveal any change in sodium values. Examination of outlier values during treatment reveal several significant OORR low values. There were 11 outliers with a serum sodium value < 126 at visit

There were 7 patients normal or low at baseline that continued to decline and had a post baseline sodium value of 125meq/L or less. The timeline of adverse events and concomitant medications for each of these 7 patients is examined, [Figure 54](#). Patient YKP3089C017- (b) (6) had low sodium values at baseline and both treatment visits where the visit 6 value was 132meq/L and the Visit 9 value was 123 meq/L. There were no adverse events related clearly to hyponatremia. The patient was on concomitant oxcarbazepine. Patient YKP3089C017- (b) (6) had low sodium values at all three samples. Baseline value was 129meq/L, Visit 6 was 126meq/L and visit 9 was 125meq/L. The patient had CNS adverse effects coded a mild and was on concomitant oxcarbazepine. Patient YKP3089C017- (b) (6) had a low baseline value, visit 6 was in reference range of 140meq/L and Visit 9 was 121meq/L. The patient was also on ongoing oxcarbazepine. Patient YKP3089C017- (b) (6) had low baseline at 128meq/L with Visit 6 and visit 9 values of 121meq/L and 132meq/L respectively. The patient had CNS adverse effects and was on concomitant oxcarbazepine. Patient YKP3089C017- (b) (6) had all three sodium values OORR low, 126, 123, 125 meq/L at baseline, Visit 6 and Visit 9 respectively. The adverse events were rash, and fatigue and the patient was on concomitant oxcarbazepine. Patient YKP3089C017- (b) (6) had a within reference range baseline but visit 6 and visit 9 were 125 and 130meq/L respectively. The were adverse effects of “hyponatraemia” and “hypocholoraemia” as well as dizziness and fatigue. The patient was also on concomitant oxcarbazepine. Patient YKP3089C017- (b) (6) had sodium values of 127, 125 and 127meq/L at baseline, visit 6 and visit 9 respectively. The only adverse effect was fatigue and the patient was on concomitant oxcarbazepine. This majority of patients in this sample had low baseline sodium and all were on the confounding concomitant AED oxcarbazepine. Examination of this sample of seven patients with the lowest serum sodium values reveals a high frequency of central nervous system adverse effects but these are confounded by the background effect of cenobamate. The temporal profile of the low sodium values does not have a consistent pattern.

Clinical Review
Steven Dinsmore, DO
NDA 212839 (cenobamate) XCOPRI

Only one patient (YKP3089C017-^{(b) (6)}) has a sequential stepwise decline from a low baseline. In the remainder the sequence is irregular, see [Figure 54](#).

Figure 54 C017, 7 Patient with at least one Post Baseline OORR low value of ≤ 125 meq/L. Profile of all Sodium Values at Baseline, Visit 6 and Visit 9.



The dataset was examined for any post baseline value minimum entries (nadir) from normal or OORR low baseline values. There were 4 (3.7%), 5 (4.6%), 9 (8.2%), and 9 (8.1%) patients in the placebo, 100mg, 200mg, and 400mg treatment arms respectively. The group mean, and median differences did not reveal a dose response, but the treatment means were lower than the placebo mean values. The minimum values from each group were lowest in the 200mg and 400mg treatment arms, [Table 68](#).

Table 68 C017, Sodium, Frequency of any post baseline minimum value (nadir) that from normal or OORR low baseline with group mean, median and minimum.

Na+, any shift from normal baseline to OORR low or OORR low baseline that had a subsequent lower (minimum) value in the post baseline period.						
Actual Arm Code	N in arm	# Pts	% Pts	Mean	Median	Minimum value in sample
Placebo	108	4	3.7	130	130	128
YKP3089 100	108	5	4.6	128	127	123
YKP3089 200	110	9	8.2	128	130	121
YKP3089 400	111	9	8.1	128	128	121

Carbamazepine and oxcarbazepine are common concomitant AEDs that may cause hyponatremia. The proportion of patients in overall study treatment arms on carbamazepine or oxcarbazepine is shown in [Table 69](#). This table reveals a small difference in exposure to confounding concomitant medication between the placebo and cenobamate treatment arms, where placebo exposure is 6% higher, [Table 69](#). Independent of a cenobamate effect on depression of sodium values, this proportionality of exposure to oxcarbazepine and carbamazepine makes it more likely that placebo arm would have the highest frequency of hyponatremia. However, this is not true and the 200mg and 400mg treatment arm have the highest frequency of hyponatremia, [Table 68](#).

An analysis is performed to determine the proportion of C017 study patients on these medications and the overlap with patients who had OORR low sodium values. It was found that there were 35 patients in study C017 with an OORR low serum Na+ at post baseline scheduled visits (Visit 6 & 9). Twenty of these 35 patients also had OORR low baseline values. Examination of the concomitant medication dataset reveals that when entries in the “ongoing” treatment variable CMENRF, or concomitant medication category variable CMCAT are positive, there were 26 patients on oxcarbazepine, 7 on carbamazepine and 2 on neither of these medications. From among these patients, a group of interest where post baseline values continued to decline from normal at baseline or low at baseline were selected. This subset consisted of 27 patients.

Concomitant treatment with oxcarbazepine or carbamazepine was examined in the 27-patient subset that had a continued trajectory of post baseline decline. All but one patient in this group was treated with concomitant oxcarbazepine or carbamazepine. The single patient not on a concomitant that can lower serum sodium was in the placebo treatment arm, [Table 70](#).

Table 69 Patients by Arm with Concomitant medication entry for CBZ-OXZ in CMENRF (dataset variable-End Relative to Reference Period) “ongoing” or CMCAT variable as “CONCOMITANT AEDS”

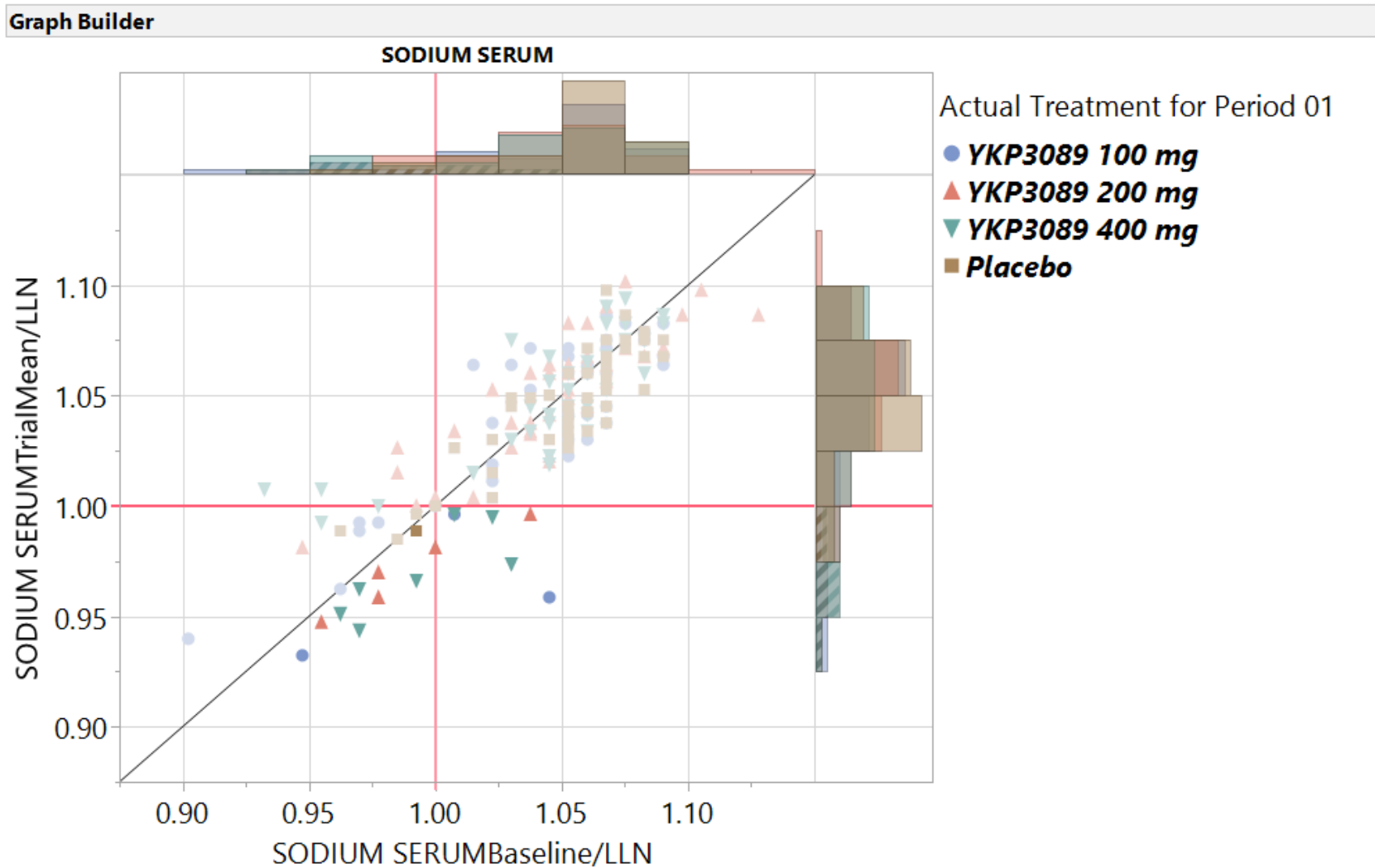
Patients by Arm with Concomitant med entry for CBZ-OXZ in CMENRF (End Relative to Reference Period) “ongoing”		
Arm	# Pts	% Pts
Placebo	51	47
YKP3089 100 mg	44	41
YKP3089 200 mg	46	42
YKP3089 400 mg	45	41

Table 70 C017, Proportion of Patients with OORR low Post-Baseline Sodium Values that were Treated with Oxcarbazepine or Carbamazepine.

Arm	n-OORR Low from Normal or Low baseline during treatment	Confounding CBZ or OXC	% On Confounding Med	% OXC	% CBZ
Placebo	4	3	75	50	25
100mg	5	5	100	100	0
200mg	9	9	100	89	11
400mg	9	9	100	66	33

From among the 182 patients on concomitant oxcarbazepine or carbamazepine among all treatment arms an analysis is performed where the mean value of both post baseline study samples was computed. These means were then examined to identify OORR low post baseline means that represented a decline from baseline, whether the baseline was normal or low. This analysis revealed 16 patients that met these criteria. From among these 16 patients only one patient was in the placebo arm, [Figure 55](#).

Figure 55 C017, Sodium Analysis: 182 Patients on Concomitant Oxcarbazepine or Carbamazepine, Distribution of Mean Post Baseline Values (visit 6 & 9)- Y Axis, Compared to Baseline Value- X Axis, Normalized to Lower Limit of Normal (133meq/L)- red axis grid lines by Treatment Arm. 45 degree line = no change, Baseline = mean post baseline value



Reviewer Comment, Sodium:

There is a high frequency of post baseline OORR low values found in patients with normal baseline values or had OORR low baseline values where decline continued. All but one of these occurrences is confounded by concomitant carbamazepine or more frequently oxcarbazepine. The single OORR post baseline low value that was not confounded by a concomitant AED that may lower serum sodium was a patient in the placebo arm. There were also several instances where the post baseline value meets CTCAE category 3 criteria.

The occurrence of post baseline OORR low values are more frequent in cenobamate treatment than in the placebo with the highest frequency in the 200mg and 400mg arms. Although all OORR low values in the treatment arms are confounded by concomitant medications, a clinically meaningful synergy between cenobamate and oxcarbazepine or carbamazepine may be possible. This is because the distribution of confounding AEDs across all treatment arms reveals the highest frequency of oxcarbazepine and carbamazepine concomitants is in the placebo arm. Labeling should have language that reflects these conditions of hyponatremia.

Chemistry Summary:

Examination of ALT values revealed one patient with a value of 7.6 x ULN that was sporadic and followed by a steady decline in values. Three were no elevations of bilirubin above the ULN. The observations on ALT values did not reach a threshold of clinical concern. There was a post baseline excess of serum potassium values that were OORR high in the cenobamate treatment arms over the placebo arm. There was maximal separation seen between the placebo and 400mg treatment arm. There were 5.6% of patients in the placebo arm with post baseline OORR high values while in the 400mg treatment arm there were 10.8% of patients with post baseline OORR high values. This should be reflected in labeling as noted in the reviewer conclusion on potassium. There was an excess of post baseline OORR low sodium values in the cenobamate treatment arms. This excess is confounded by concomitant treatment with oxcarbazepine or carbamazepine in all cases. This observed excess is not in alignment with the overall distribution of oxcarbazepine and carbamazepine concomitant treatment in the overall study population where there was an excess of oxcarbazepine and carbamazepine treatment in the placebo treatment arm. Thus, an independent effect of cenobamate on the decline in serum sodium values appears to be present. This should be reflected in section 6 of labeling as identified in the reviewer comment on sodium (above).

8.4.8. C013-C017 OLE (Sponsor Presentation) Open Label Extension Period

Hematology

Means

In the long term there was a decrease in platelets throughout the timepoints up to 36 months that did not reach a clinically meaningful level. Thereafter a small mean increase in platelet counts was noted.

Shifts

For the majority of hematology parameters shifts from normal baseline values to abnormal values were limited to 5 or fewer subjects. This was noted at any timepoint post baseline. No clinically meaningful trends were observed in shifts from baseline normal to abnormal values at post baseline timepoints.

Outliers

The majority of subjects' hematology parameters had a reported maximum post-baseline intensity of mild (CTCAE grade 1) for decreased lymphocytes and platelets. For decreased neutrophils, subjects had similar maximum post-baseline intensities of mild and moderate for both the cenobamate DB to OLE and placebo DB to cenobamate OLE groups. Subjects had a reported maximum post-baseline intensity of severe (CTCAE grade 3) for the following parameters:

- Decreased hemoglobin: 1/340 (0.3%) subject in the cenobamate DB to OLE group
- Decreased lymphocytes: 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group
- Decreased neutrophils: 5/340 (1.5%) subjects in the cenobamate DB to OLE group and 4/162 (2.5%) subjects in the placebo DB to cenobamate OLE group
- Decreased platelets: 1/338 (0.3%) subject in the cenobamate DB to OLE group and 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group

One/340 (0.3%) subject in the cenobamate DB to OLE group had a potentially life-threatening (CTCAE grade 4) post-baseline decreased neutrophil.

Chemistry

Slight mean or median changes from baseline to post-baseline LFTs did not show a clinically meaningful trend. A slight increasing trend in blood urea nitrogen and a slight decreasing trend in creatinine were observed for both treatment groups.

For the majority of clinical chemistry parameters, shifts from normal baseline values to abnormal values over time were limited to 5 or fewer subjects in the cenobamate DB to OLE and placebo DB to cenobamate OLE groups. Although no clinical trends were observed in shifts from baseline normal values to abnormal values at analysis timepoints by post-baseline and at any time post-baseline, ALP had the most frequent slight shifts from normal baseline values to high in both treatment groups (cenobamate to OL and placebo to OL).

Two (0.6%) subjects in the cenobamate DB to OLE group and 1 (0.6%) subject in the placebo DB to cenobamate OLE group had AST of $\geq 3x$ ULN, while 2 (0.6%) subjects in the cenobamate DB to

OLE group and 2 (1.2%) subjects in the placebo DB to cenobamate OLE group had ALT of $\geq 3x$ ULN. There was 1 (0.6%) subject with total bilirubin of $\geq 2x$ ULN and 2 (1.2%) subjects with ALT of $> 5x$ ULN in the placebo DB to cenobamate OLE group. One (0.3%) subject in the cenobamate DB to OLE group had ALP $> 2x$ ULN.

The following clinical chemistry results were reported to have a maximum post-baseline intensity of severe (CTCAE grade 3):

- Increased ALT: 2/162 (1.2%) subjects in the placebo DB to cenobamate OLE group
- Decreased glucose: 1/340 (0.3%) subject in the cenobamate DB to OLE group and 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group
- Increased glucose: 2/340 (0.6%) subject in the cenobamate DB to OLE group
- Increased creatinine: 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group
- Increased direct bilirubin: 1/340 (0.3%) subject in the cenobamate DB to OLE group
- Decreased phosphate: 6/340 (1.8%) subjects in the cenobamate DB to OLE group and 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group
- Increased potassium: 1 (1/340 [0.3%]) subject in the cenobamate DB to OLE group and 1/162 (0.6%) subject in the placebo DB to cenobamate OLE group
- Increased sodium: 1/340 (0.3%) subject in the cenobamate DB to OLE group
- Decreased sodium: 18/340 (5.3%) subjects in the cenobamate DB to OLE group and 6/162 (3.7%) subjects in the placebo DB to cenobamate OLE group

One/340 (0.3%) subject in the cenobamate DB to OLE group had a potentially life-threatening (CTCAE grade 4) post-baseline decreased glucose

Abnormal Clinical Chemistry Parameters Reported as Adverse Events – OLE Pool

Hyponatremia- and reduced serum sodium-related AEs were reported in 4/504 (0.8%) subjects receiving cenobamate. Although 24/502 (4.8%) subjects had a severe (CTCAE grade 3) post-baseline decreased sodium value (Appendix C, Table 7.9.3), only 1 SAE.

C021

Strategy

The strategy for review of study C021 hematology and clinical chemistry laboratory parameters will be to enter the sponsor overview analyses followed by a screening of core laboratory parameters using JMP clinical shift plot of mean post baseline values to screen for notable divergence in the cenobamate treatment interval. There will be a detailed exploration where a possible treatment effect has been noted in the placebo-controlled intervals of studies C013 and C017 as well as the phase 1 studies. These parameters will include hemoglobin, leukocytes, neutrophils, serum potassium and sodium.

Hematology

Sponsor Presentation (ISS p 126):

During Study YKP3089C021, there were no clinically meaningful trends in mean changes from baseline at each visit for any hematology variables. Percentage eosinophils, monocytes, lymphocytes, and erythrocyte distribution width percentage remained higher than baseline values for most of the treatment period for all safety evaluable groups at each visit. Erythrocyte counts, hematocrit, hemoglobin, leukocyte counts, lymphocyte counts, neutrophil counts and percentages, and platelet counts remained lower than baseline values for most of the treatment period for all safety evaluable groups. One AE each of anemia, eosinophilia, platelet count decreased (all from the Cenobamate and Other Concomitant AEDs group), and eosinophil count increased (from the Cenobamate and phenytoin group) led to study treatment discontinuation. None of these AEs were considered severe or serious. None of the AEs had an outcome of death.

By-visit shifts in percentage eosinophils, mean corpuscular volume, erythrocyte distribution width percentage, percentage lymphocytes, mean platelet volume, and percentage monocytes trended to higher from normal at baseline. By-visit shifts in mean corpuscular hemoglobin concentration, erythrocyte counts, leucocyte counts, and neutrophil counts trended to low from normal at baseline. In general, the number of shifts to either high or low values relative to the overall numbers of samples at any visit was very low. Although there were frequent shifts of the erythrocyte distribution with percentage to high from normal, the mean increases at any visit were low (1% to 3%), and mean levels at each visit were similar to the mean baseline levels.

Reviewer Assessment

The mean value of all post baseline study measurements are computed and examined for post baseline shift of the value normalized to either upper limit of normal or lower limit of normal

for screening, this method is presented in the JMP clinical application used in this analysis. One examination each is performed for the upper boundary and the lower boundary of normal values. Outlier patients identified by OORR values are explored to examine trends in values over the study timeline and associated adverse events.

Basophils: there are no post baseline mean values above the ULN

Eosinophils:

>ULN: One patient (YKP3089C021-^{(b) (6)}) is identified where with a mean post baseline eosinophil value that was above the ULN and also greater than the baseline value. This patient had an elevation of eosinophils on day 29 to 1100 /mm³. The value returned to normal limits on day 44. This patient discontinued the study due to a seizure on day 44.

Erythrocytes:

>ULN: There were 6 patients with a normal baseline and a mean baseline value the was OORR high. The maximum mean value was 1.037 x ULN. This observation does not indicate a shift to erythrocytosis.

Hemoglobin:

>ULN: There were two patients with a normal baseline value that had a mean of post baseline measurements that was > ULN. The maximum value was 1.017 x ULN.

<LLN: There was an excess of patients where the mean of post baseline values was less than the baseline value. This is expressed as a negative change in 730 (56%) patients and a positive change in 579 (44%) patients. There were 20 (1.5%) patients with a post baseline mean of measurements that was lower than their baseline value whether that baseline value was within reference range or OORR low. These declines were generally less than 1.0g/dl and reached a plateau rather than maintaining a decline in slope.

Two patients are identified that have a consistent post baseline decline, patients YKP3089C021-^{(b) (6)} and YKP3089C021-^{(b) (6)} Patient YKP3089C021-^{(b) (6)} had a low baseline hemoglobin with an underlying history of microcytic anemia identified approximately 4 months prior to study entry. Hemoglobin at baseline was 9.8g/dl. Hemoglobin had a steady decline to 7.5g/dl by study day 139 and the treatment was discontinued. There was improvement in hemoglobin to a value of 8.6g/dl 14 days after cenobamate discontinuation. Patient YKP3089C021-^{(b) (6)} had a progressive and sequential decline in hemoglobin from a baseline value of 13.3g/dl to a post baseline to a value of 7.5g/dl on study day 202. Cenobamate 200mg/day was continued. There was an increase in value to 14.5g/dl on study day 267 with further improvement to 15g/dl on study day 365 while continuing on cenobamate 200mg daily.

Lymphocytes:

>ULN: there were 11 patients with a normal baseline lymphocyte value where the mean of post baseline values was above the ULN. The maximum of these values was $9.1 \times 10^9 /L$ (RR 0.9-3.6 x $10^9/L$). this was the only post baseline value on study day 15. The patient discontinued for reason other than adverse event. In 4 patients there was sustained lymphocyte values > ULN. In 4 of the 11 patients a rash relate adverse event is entered. In one of the 11 patients where was an adverse event of eosinophilia.

<LLN: There was an excess of patients where the mean of post baseline values was less than the baseline value. This is expressed as a negative change in 827 (63%) patients and a positive change in 479 (37%) patients. There were 8 (0.6%) patients with a post baseline mean of measurements that was lower than their baseline value whether that baseline value was within reference range or OORR low.

Monocytes

>ULN: there was one patient with normal baseline monocyte value that had a mean of post baseline value > ULN. This patient YKP3089C021- (b) (6) also had an adverse event entry for eosinophilia and had a mean post baseline elevation of lymphocytes.

Neutrophils

>ULN: There were 5 patients with a normal baseline neutrophil value and post baseline mean of values > ULN. One (YKP3089C021- (b) (6)) of these 5 patients has an entry of "eczema" with elevation > ULN at 7 of 9 post baseline measurements. One of the five patients (YKP3089C021- (b) (6)) with a maximum lymphocyte value of $10.4 \times 10^9/L$ (lab day 50 during follow up) from a baseline of $3.8 \times 10^9/L$ developed angioedema on study day 4 and discontinued from the study with last treatment on study day 4. Lymphocyte value on day 3 post treatment was $5.9 \times 10^9/L$. Two patients had sustained lymphocyte values > ULN (YKP3089C021- (b) (6) YKP3089C021- (b) (6)). The first, as noted above had an entry for "eczema", the second had entries for "dizziness" and "headache". No pattern of adverse events is associated with the shift high of lymphocyte values. The patient with angioedema did not have an OORR high value until 46 days after cenobamate discontinuation and is not clearly related.

<LLN: There was an excess of patients where the mean of post baseline values was less than the baseline value. This is expressed as a negative change in 778 (60%) patients and a positive change in 528 (40%) patients. There were 6 (0.46%) patients with a post baseline mean of measurements that was lower than their baseline value whether that baseline value was within reference range or OORR low.

Leukocytes

>ULN: Visual inspection of the distribution of baseline (x axis) to mean of post baseline values (y-axis) reveals the distribution of plot points around a line of slope=1, (no change from baseline to trial mean) has an excess of points to the right of the no change line. This distribution indicates there are more patients whose post baseline measurements mean value

less than baseline than the frequency of patients whose post baseline mean is greater than baseline. There were 8 patients with a post baseline mean that was OORR high and greater than baseline. The adverse events of these 8 patients are examined and three are found to have preferred term entries that can be due to hypersensitivity. One patient had an entry for “eczema”, a second patient had an entry for “rash pruritic”, and a third patient had an entry for “angioedema”. None had persistent infections.

<LLN: There was an excess of patients where the mean of post baseline values was less than the baseline value. This is expressed as a negative change in 814 (62%) patients and a positive change in 495 (38%) patients. There were 24 (1.8%) patients with a post baseline mean of measurements that was lower than their baseline value whether that baseline value was within reference range or OORR low. The leukocyte values and associated adverse events of these 24 patients were examined. One patient (YKP3089C021- (b) (6)) had an adverse event entry for “leukopenia” that spanned study day 43 to approximately study day 620. A “urinary tract infection” spanned study day 50 to approximately 110. The leukocyte count plateaued in the range of 3.0 to 2.4 from study days 15 to 632. A second patient (YKP3089C021- (b) (6)) had a peak decline of $3.6 \times 10^9/L$. The overall trend among these 24 patients was a decline of not more than $1 \times 10^9/L$ that tended to plateau. There were viral infection adverse event entries in (including influenza and upper respiratory infection) in 6 of the 24 and bacterial infection (including urinary tract infection) in 2 of the patients.

Reviewer Comment: A decline in neutrophil count from baseline is common and in alignment with the observations from the pivotal studies. In this extended exposure study the decline tended to plateau and was not commonly $> 1.0 \times 10^9/L$ from baseline.

Platelets

>ULN: Visual inspection reveals a symmetric distribution of plot points around a line of slope=1, (no change from baseline to trial mean). There were 4 patients with a normal baseline and a mean of post baseline values $> ULN$. The maximum value was $1.18 \times ULN$. This patient (YKP3089C021- (b) (6)) had a maximum platelet count of $442 \times 10^9/L$. There was an adverse event entry for “rash pruritic” and cenobamate was discontinued after 4 days of treatment. The high platelet count was captured in follow up on study day 20. A maximum platelet value of $707 \times 10^9/L$ was captured from patient YKP3089C021- (b) (6) in follow up at 111 days after last cenobamate treatment. This patient had a mean post baseline platelet value of $1.037 \times ULN$. This patient (YKP3089C021- (b) (6)) had an entry of urticaria on day 344, 83 days after last cenobamate treatment. The relationship between the delayed urticaria and thrombocytosis after cenobamate treatment is uncertain. None of these four patients had an adverse event entry for a prothrombotic event.

<LLN: In alignment with the visual inspection of the distribution noted in the paragraph above, there were 602 (46%) patients with a mean of post baseline measurements that were higher than baseline and 696 (54%) patients with a post baseline mean that was less than baseline.

There was 1 patient with a baseline within reference range that had an OORR low mean post baseline value.

Reviewer Comment: The platelet count is generally stable from baseline to post baseline across the study measurements.

Erythrocyte Distribution Width (RDW)

>ULN: Visual inspection of the baseline to post baseline mean value plot reveals a trend toward post baseline mean > baseline RDW value. All patients with a post baseline mean > 1.2 x ULN (n=37) that was elevated over baseline mean were examined for distribution among the post baseline mean plots of eosinophils, lymphocytes, leukocytes, and neutrophils. The adverse event profile, serum ALT and globulin values were evaluated in this 37-patient subset. There was no pattern of adverse events or consistent relation to ALT values or serum among these patients.

Reviewer Comment: RDW is a measure of the variability in the size of circulating red blood cells (RBCs) and is derived from automated hematology analyzers. RDW reflects the heterogeneity of erythrocyte volume and mean corpuscular volume (MCV) and is characterized as an electronic equivalent of erythrocyte anisocytosis as is registered light-microscopically in blood smears. RDW is a coefficient of variation of erythrocyte volume (in percentage, %), RDW expresses the dispersion of the RBC volume curve. There have been recent studies that show an association between inflammation, oxidative stress, negative outcome in vascular diseases and an increased RDW. The trend to post baseline increase in RDW seen during cenobamate treatment is of interest due to the pro-hypersensitive properties of cenobamate. It is reasonable to query if this pro-hypersensitive potential translates into a pro-inflammatory property. Exploration of the RDW trend in study C021 did not reveal substantive associations with inflammatory events.

Hematology Reviewer Summary:

There were an excess of post baseline declines in hemoglobin, lymphocytes, neutrophils, and leukocytes. The decline in all four parameters tended to plateau rather than follow a trajectory of continuing sequential decline. Associated adverse events were uncommon. Based on data from the pivotal studies labeling should include the decline seen in neutrophils and leukocytes. Red cell distribution width increased post baseline. There was no association with a change in eosinophils, lymphocytes, leukocytes, and neutrophils. The cause is unclear.

Chemistry

Sponsor Presentation (ISS p 132):

During Study YKP3089C021, all mean changes in serum chemistry variables were small and not clinically meaningful. Mean levels of ALT, AST, BUN, and glucose at each visit trended slightly higher compared to baseline over the course of treatment. Bilirubin, calcium creatinine

clearance, direct bilirubin, and sodium trended lower over the course of treatment. The remainder of the serum chemistry variables showed no change over time. One AE each of alanine aminotransferase increased, hepatic enzyme increased and hepatic function abnormal led to study drug discontinuation. None of these AEs were considered severe or serious. And none of the AEs had an outcome of death. By-visit shifts in creatinine and globulin trended to low from normal at baseline and shifts in creatinine clearance trended to high from normal at baseline but in general, the number of shifts to either high or low values relative to the overall numbers of samples at any visit was very low.

Reviewer Assessment

Alkaline Phosphatase (ALP)

>ULN: there were 35 patients that had a baseline ALP value within reference range where the mean of post baseline values was OORR high. The laboratory and adverse event data from 5 patients with a post baseline mean $> 1.2 \times$ ULN are examined. One patient, YKP3089C021- (b) (6) had a trend of increasing values to study day 117 that did not exceed $2 \times$ ULN. There was an adverse event entered for “hepatic function abnormal” (the only adverse event). The maximum ALT value for this patient was $3.05 \times$ ULN and maximum AST was $4.07 \times$ ULN with maximum bilirubin within reference range of $0.8 \times$ ULN.

Alanine Aminotransferase (ALT)

>ULN: there were 42 patients with a baseline ALT within reference range that had a mean of post baseline values that was OORR high. the maximum mean post baseline value was $2.7 \times$ ULN while there were 5 patients with a post baseline mean of $>$ than $1.9 \times$ ULN. Three of these five patients had AST post baseline mean values that were OORR high between 1.4 and $1.72 \times$ ULN. The complete set of post baseline individual values of ALT, AST, and Bilirubin are examined for these 5 patients. Four patients (YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6)) have sporadic elevations of ALT with no elevation of Bilirubin greater than $0.63 \times$ ULN, see [Figure 56](#) and [Figure 57](#). One patient, YKP3089C021- (b) (6) had a concurrent elevation of ALT, AST, ALP and bilirubin. This patient was found to have cholelithiasis and biliary sludge. A cholecystectomy was performed with subsequent resolution of the laboratory abnormalities. The timeline of laboratory studies and surgery date are shown in [Figure 58](#). This figure reveals return of AST and bilirubin to reference range in alignment with the surgical procedure while cenobamate (YKP) treatment remains ongoing with escalating dose.

Figure 56 C021 Four Patients with Maximum Mean Post Baseline ALT, Profile of ALP, ALT and AST by Study Visit with ALT ULN 33 U/L (YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6))



Figure 57 C021 Four Patients with Maximum Mean Post Baseline ALT, Profile of Bilirubin by Study Visit with ULN 1.1mg/dl
 (YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6) YKP3089C021- (b) (6))

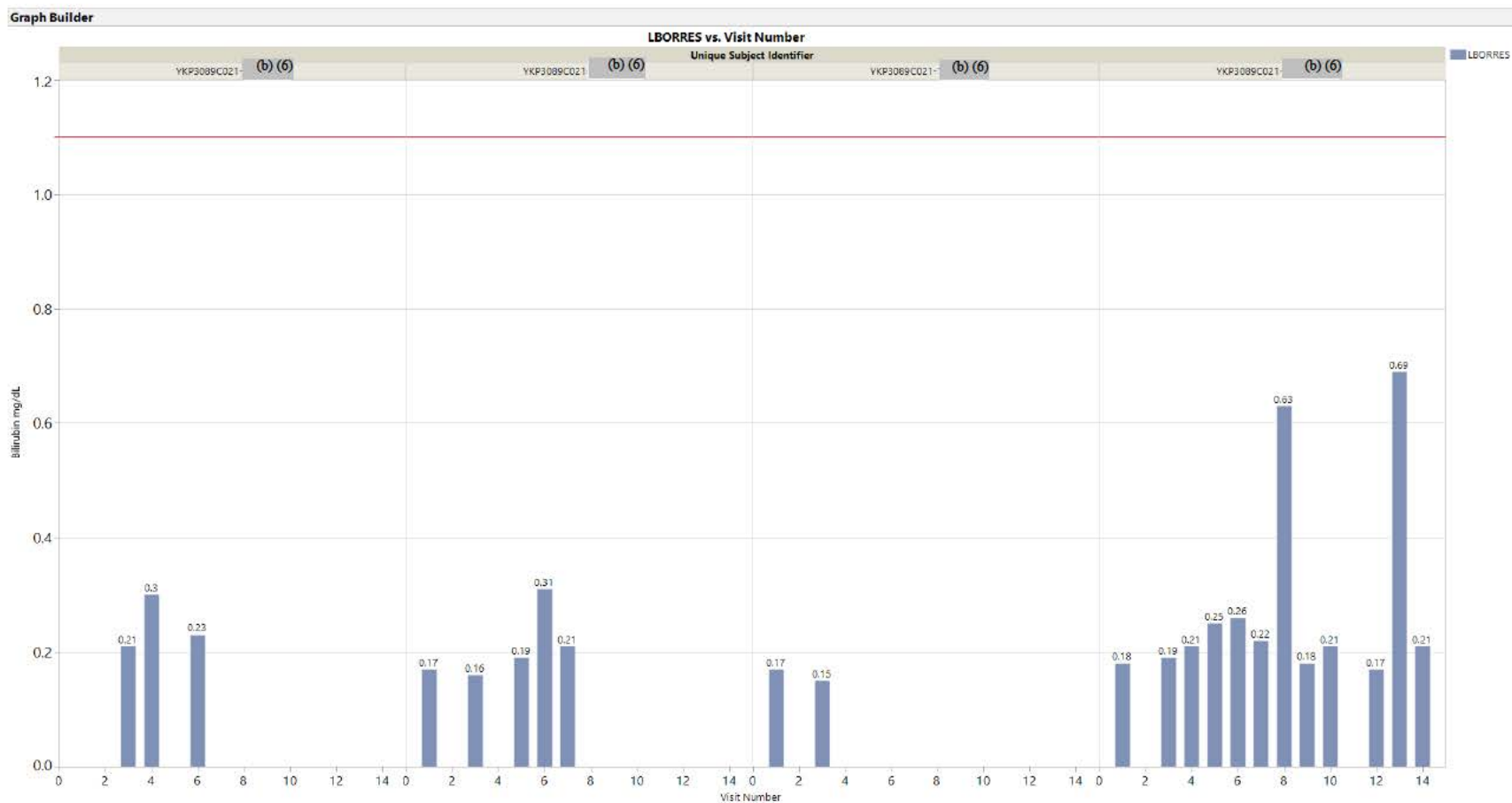
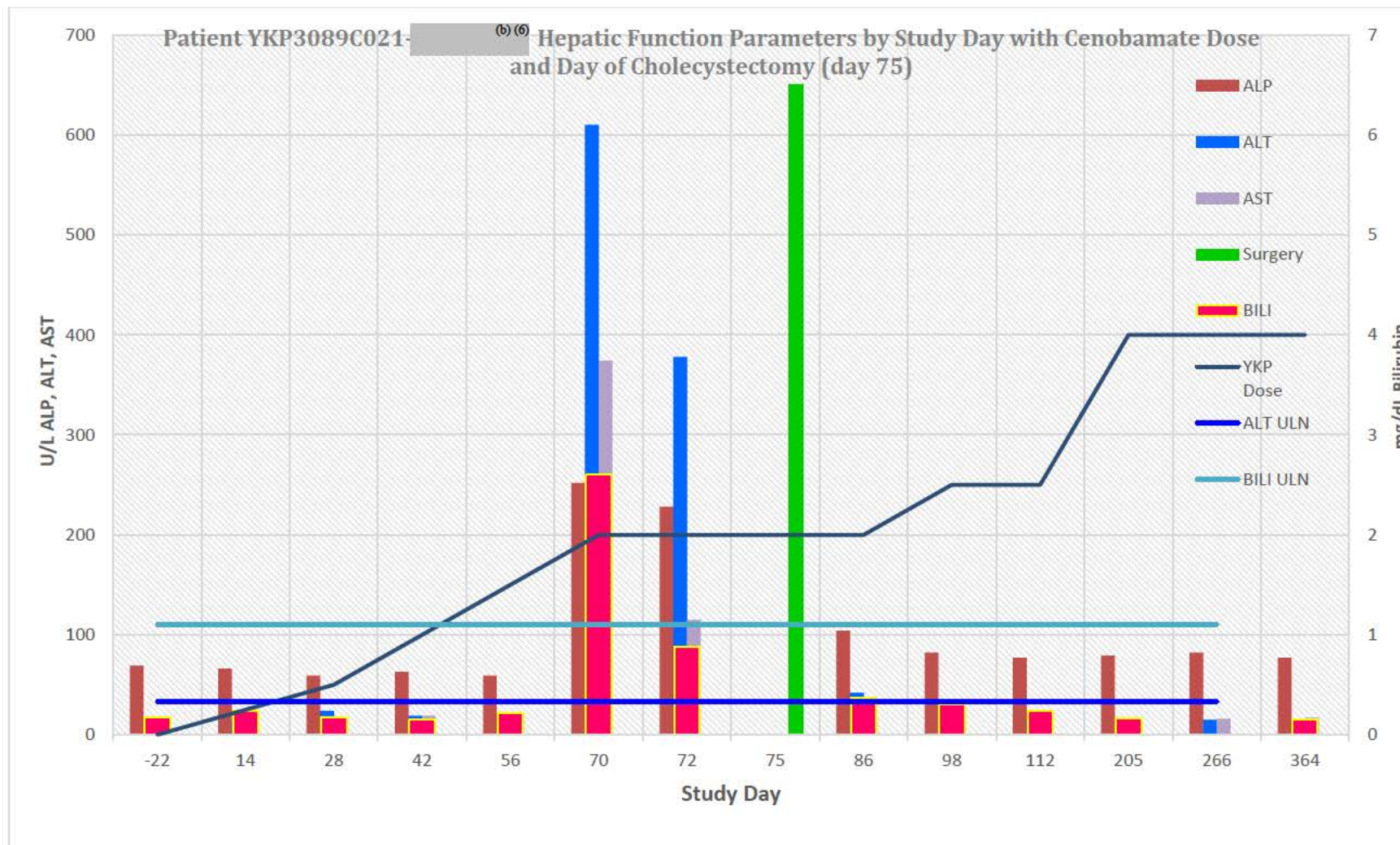


Figure 58 C021, Patient YKP3089C021- (b) (6) Elevation of ALT and Bili, Shown with all Hepatic Function Parameters, Cenobamate Dose and Day of Cholecystectomy by Study Day



All patients with an OORR high mean of post baseline values that may have a baseline value within reference range or a baseline that was elevated are identified for further screening of concurrent AST, ALP or bilirubin abnormalities. There were 59 patients identified. Five of these patients were evaluated as high mean outliers in the discussion above. There are 54 patients remaining. From among these patients there was a single patient with a bilirubin greater than the ULN. This patient had a bilirubin value of 1.39 mg/dl (1.27 x ULN). This patient was also found to have a maximum post baseline ALT value of 333 U/L (11 x ULN), an AST value of 478 U/L (13.3 x ULN) and an ALP value of 345 U/L (3 x ULN). There is an adverse effect entry for “hepatic enzyme increased”. There is an SAE entry for “seizure” on study day 434 while the ALT elevation occurs on day 42. The complete timeline of laboratory values reveals the patient has a persistently elevated ALP, while the serum bilirubin, ALT and AST return to reference range values at the subsequent Visit 6 study measurements of day 54, see [Figure 59](#).

Among the remaining 53 patients, there were 49 patients with a maximum post baseline ALP value that was greater than baseline value, and 22 of these values were OORR-high. The adverse event profile of these 22 patients was examined. No clear pattern emerged. There were no events involving gall bladder or bone associated with the ALP elevations. From among these 22 patients there were 9 patients with persistent elevation of ALP during the course of the study. Adverse events were examined for possible related medical issues. Among these 9 patients one had an adverse event of “bone pain”, a second had an adverse event of “limb injury” and a third had an event of “vitamin D deficiency”.

AST values among these 53 patients reveals that 6 patients had a post baseline maximum value that was > 3 x ULN. The laboratory profile of these six patients is examined. Patient YKP3089C021- (b) (6) has a single, sporadic OORR high elevation that is 3.7 x ULN. There are no OORR high bilirubin values during the study. There are multiple OORR high ALT and ALP values. Patient YKP3089C021- (b) (6) has persistent elevation of AST to OORR high during the study and concurrent elevations of ALT to OORR high but no elevation of bilirubin values. Patient YKP3089C021- (b) (6) has a single elevation of AST to 478 U/L (13.2 x ULN) on study day 714 associated with an elevation of ALT to 245 U/L (7.4 x ULN). The exposure dataset indicates the last treatment with 400mg cenobamate on study day 621. Based on the taper interval described in protocol YKP3089C021 Amendment 4, July 28, 2017 the last dose of cenobamate 100mg is projected to have occurred on study day 642. The AST and ALT elevation occurred 72 days after last dose of cenobamate. The relationship is uncertain and unlikely due to the absence of temporal relationship. Patient YKP3089C021- (b) (6) had a single OORR high elevation of 477 U/L on study day 42 with associated increases in ALT and ALP but no elevation of bilirubin. Patient YKP3089C021- (b) (6) had intermittent elevations of AST. There were associated elevations of ALT but no OORR high elevations of bilirubin. The maximum elevation of AST occurred on study day 274 that occurs 66 days after final cenobamate treatment where the preceding value on study day 211 (treatment end date is 207) was normal. Again, there is no temporal relationship to cenobamate treatment and the 4 day post treatment value was within reference range. Patient YKP3089C021- (b) (6) had

persistent elevation of AST during the course of the study (to study day 182) with multiple OORR high elevations of ALT and ALP also present. There is no OORR high bilirubin value. The past medical history reveals “cirrhosis alcoholic”. The persistent elevations are likely related to the underlying hepatic disease.

Figure 59 YKP3089C021- (b) (6) Patient with Sporadic Outlier OORR-High Values for ALT and Bilirubin with Concurrent OORR High AST and ALP.



Reviewer Comment, ALT:

There were 308 (23.4%) patients with a post baseline maximum value for ALT during the course of the study that were OORR high and were an increase from the baseline value. The extreme outliers are examined. A trend to sustained and sequential elevation of ALT values is generally not present. There was a single patient with an elevation of ALT to 18.5 x ULN with an elevation of bilirubin to 2.4 x ULN. This patient had an obstructive biliary lesion identified by ERCP and an elevation of ALP to 2.2 x ULN is in alignment with this finding. The abnormalities resolved after cholecystectomy. There were no Hy's law cases in the C021 laboratory dataset and no signal for sustained and sequential escalation of ALT.

Aspartate Aminotransferase (AST)

>ULN

There were 8 patients with at least one post baseline AST value that was > 3 x ULN. Four of these patients had an ALT post baseline value > 3 x ULN but none had bilirubin values > ULN. Three of these eight patients had sustained elevations of ALT, however all elevations were less than 2 x ULN except one in each of the three cases. There is no evidence for clinically substantive elevations of AST associated with cenobamate treatment.

Bilirubin

>ULN

One patient had an elevation of bilirubin > 2 x ULN. This elevation occurred in the context of biliary tract outlet discussed above, patient YKP3089C021- (b) (6). Seventeen (1.4%) patients had at least one bilirubin value > ULN. The bilirubin profile of these patients is examined and in 15 of the seventeen the elevation was a single, sporadic event. In one of the remaining patients there were 4 elevation > 1 x ULN but less than 2 x ULN. The measurements were within reference range for all values after study day 56. There were no associated adverse events entered. The second remaining patient had two values, on study day 29 of 1.22 x ULN and the second on study day 208, 1.7 x ULN. All intervening values were within reference range. There is no signal for elevation of bilirubin associated with cenobamate treatment.

Calcium

>ULN: There were 26 patients with a maximum post baseline calcium value > ULN where baseline was normal. The maximum value from among these OORR high values was 11.1mg/dL where the ULN is 10.5mg/dL.

<LLN: There were 161 patients with a minimum post baseline calcium value of less than the LLN where baseline was within reference range. From among these there were 9 patients identified with a minimum calcium post baseline value less than 0.85 of the LLN. This subset of patients with calcium values < 7.2mg/dL are examined and 8 of nine cases the OORR low value was a single sporadic event. The remaining patient, YKP3089C021- (b) (6) had three OORR low post baseline values, [Table 71](#). The patient with the single, sporadic lowest value had an entry

of 4.5mg/dL (0.53 x LLN) on study day 141 with all prior value within reference range and no declining trend. There is no clinically sustentative occurrence of low calcium values.

Table 71 C021, Calcium, Patient YKP3089C021- (b) (6), 3 entries OORR Low.

Calcium	YKP3089C021-01067121	
VISIT	LBDY	Ca++ mg/dL (range 8.5-10.5 mg/dL)
Visit 1	-14	8.5
Visit 3	15	8.4
Visit 4	29	9
Visit 5	43	8.4
Visit 6	56	8.9
Visit 7	71	8.7
Visit 8	85	8.9
Visit 9	103	6.9
Visit 10	118	9
Visit 12	211	8.6
Visit 13	274	8.7
Unscheduled Visit	281	8.9

Reviewer Comment, calcium: there are more frequent OORR low post baseline calcium values than OORR high values. Examination of the OORR low subset < .85 LLN does not reveal sequential decline in value over sequential study visit samples. The majority of low values were isolated sporadic events. The patient with the highest frequency of OORR low values < .85 LLN had three low entries separated by reference range values. There is a higher frequency of post baseline OORR low calcium values, but the most severe subset of these entries does not reveal a clinically substantive trend toward low calcium values.

Chloride

>ULN: there were no mean post baseline chloride values OORR high.

Creatinine

>ULN: there were 5 patients where the mean of all post baseline values was OORR high. Four of these five patients had baseline creatinine values that were OORR high. The profile of individual creatinine values across the study timeline for each of these five patients is examined. As noted, 4 of the five patients had a baseline high serum creatinine. Two of these 4 patients had a mean post baseline creatine value that was lower than the baseline value (while remaining OORR high), in one of the 4 patients there was no change in the mean of post baseline creatinine values and the baseline value and in the remaining patient the mean of post baseline values had an elevation over the baseline value. This patient (YKP3089C021- (b) (6)) had a baseline creatinine of 1.8 mg/dL (RR, 0.7 -1.4 mg/dL) with subsequent peak elevation to 2.4 mg/dL during treatment, although the majority were values of 2.2 to 2.3 mg/dL. The maximum value seen was at the 6-month post treatment follow-up visit where creatinine value was 2.9 mg/dL. This patient had a urinary tract infection at approximately study day 63 with no other

potential renal related disorder. The patient completed the study without an SAE or discontinuation. The 5th and remaining patient (YKP3089C021- (b) (6)) with an OORR high mean of post baseline creatinine values had a normal baseline value. This patient has a medical history entry of “chronic kidney disease”. There were two OORR high values during the study, the 1st at visit 4, study day 28 to a value of 1.5 mg/dL, (RR 0.7 – 1.4 mg/dL) the second OORR high entry is at termination visit, study day 161 with a creatinine value of 2.6mg/dL. Study discontinuation was associated with urosepsis and treatment with gentamycin.

To further explore elevations in creatinine patients with maximum elevations of post baseline serum creatinine are examined. There were 5 patients with a maximum post baseline elevation > 1.4 x ULN. Two of these patients were captured by the analysis of the mean of post baseline values (YKP3089C021- (b) (6) YKP3089C021- (b) (6)). The remaining three patients each had sporadic, single elevation of creatinine to OORR high with no concurrent adverse effects associated with chronic kidney disease. One of these three patients had a medical history of “pyelonephritis chronic”.

Reviewer Comment, creatinine: The frequency, severity, clinical course and temporal relationship of elevated serum creatinine is examined and does not reveal a clinically substantive effect of cenobamate treatment on creatinine values.

Globulin

>ULN: There are 4 patients where the mean of post baseline globulin values is OORR high and represents an increase from the baseline value. The maximum mean post baseline value is 1.07 x ULN. The individual globulin values over the course of the study is examined. The maximum post baseline globulin is 5.1 g/dL, one other post baseline value among these patients over 4.0g/dL occurred. All of the remaining values were less than 4.0 g/dL (RR 2.3 – 3.5 g/dL).

The maximum post baseline globulin values are examined to capture OORR high post baseline globulin values that represent an increase from baseline. There were 49 (3.7%) patients that met these criteria.

<LLN: there are 124 patients where the mean of post baseline globulin values is OORR low and represents a decline from the baseline value. The lowest post baseline change from baseline for all patients is examined. There were 44 patients with at least one post baseline value that was ≥8g/dL from the baseline value. The Adverse events of these patients was examined for

From among these 44 patients there were 16 entries in the “Infections and infestations” SOC from 13 patients (30% of 44 pts). The most frequent preferred terms from these 16 entries were “influenza” with 3 entries, “upper respiratory tract infection” with 3 entries, and “viral upper respiratory tract infection” with 2 entries. The remaining 8 preferred terms had a single entry each.

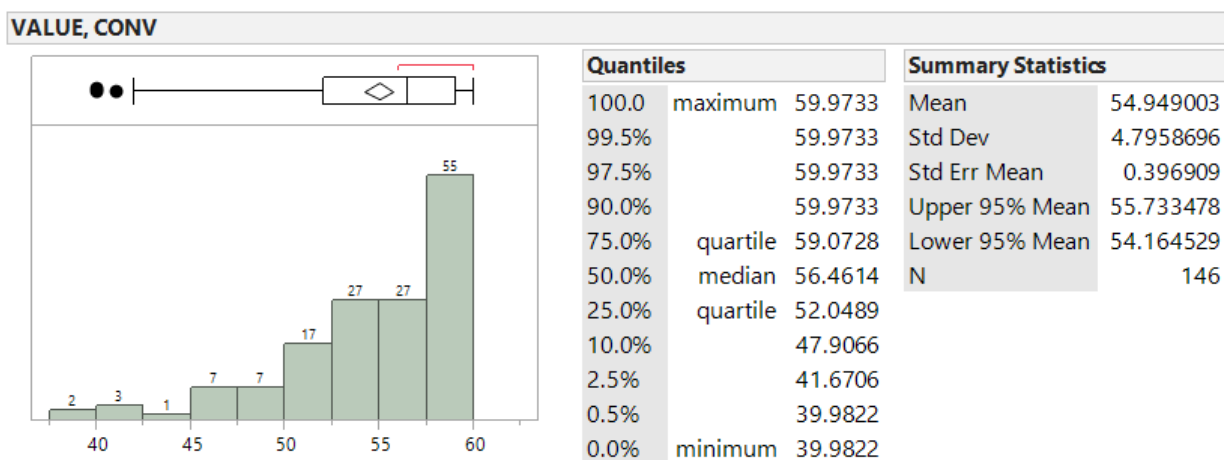
The minimum post baseline globulin values are examined to capture OORR low post baseline globulin values that represent a decrease from baseline. There were 576 (44%) patients that met these criteria.

Reviewer Comment, globulin: There was a clear trend toward a decline of globulin values during cenobamate treatment. The clinical significance of this observation is uncertain.

Glucose

Examination of the ADLB dataset reveals the OORR high value for glucose is set at 200mg/dL. No OORR low limit value is assigned in the STDM or ADAM dataset. The variable LBNRIND (reference range indicator) has only 3 “LOW” entries for post baseline glucose values. The values represented as low are 24mg/dL, 29mg/dL and 32mg/dL. Above 40 mg/dL the variable entries are “NORMAL”. Normal entries begin at 40mg/dL and remain normal until above values of 200mg/dL where “HIGH” is entered. “Normal” includes 146 entries from 95 patients with value between 40mg/dL and 60mg/dL with the distribution and counts shown in [Figure 60](#). Based on the examination in the ADLB dataset the reference range values for blood glucose appear to be 40mg/dl for the lower boundary and 200mg/dL as the upper boundary.

Figure 60 C021, ADLB dataset for Glucose, Distribution of Entries for Glucose Values from 40mg/dL up to and including 60mg/dL with Mean and Median.



The unusually broad reference range for glucose is cause for close scrutiny of this laboratory parameter. The glucose dataset is examined with reference range boundaries set by the reviewer as 65mg/dL for the lower boundary and 150mg/dL for the upper boundary. The upper boundary is above the range for fasting glucose and above typical 2 hour post prandial glucose because the prandial status of patients at each study clinical chemistry sample may vary.

>ULN: (RR 65 – 150mg/dL)

Mean Post Baseline: with the adjusted boundary for OORR high glucose there were 10 (0.76%) patients identified where the mean of post baseline glucose values is > 150mg/dl that represented an increase value over baseline.

Maximum Post Baseline Entry: There were 67 (5.1%) patients with a maximum post baseline value greater than 150mg/dL that represented an increase over baseline value. There were 25 patients from this subset with at least one post baseline value > 200mg/dL.

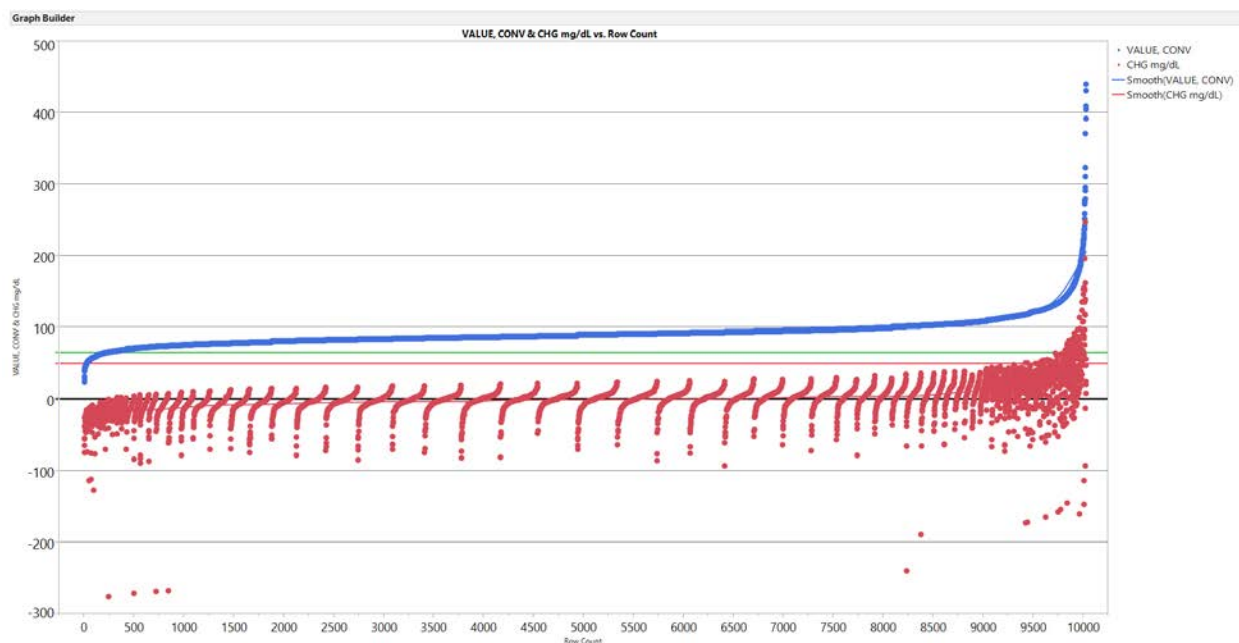
<LLN:

Mean Post Baseline: There were 6 (0.46%) patients identified where the mean of post baseline glucose values is <65mg/dl that represented a decrease value from baseline.

Minimum Post Baseline Entry: There were 162 (12.3%) patients with a minimum post baseline glucose value less than 65mg/dL that represented a decrease from baseline value. There were 63 instances from 44 patients with at least one post baseline value of ≤ 55 mg/dL that represents a decline from baseline.

An analysis of glucose values from all patients with 7 or more visits from the 1 year study timeline, representing 1152 patients with 10030 glucose laboratory entries is performed to evaluate the distribution of glucose values. This method proved near equal contribution of samples from each patient. This analysis excluded patients with 6 or fewer study visits. Those patients contributed 9 of 221 glucose values < 65mg/dL, thus the remaining sample will only lose approximately 4.1% of the information from instances of OORR low glucose values but will retain a more representative distribution of values from patients with longer participation in the study and a higher frequency of instances per patient of glucose sampling. This analysis reveals the proportion of positive change from baseline is nearly equal to negative change from baseline, where there are 49% of entries with a positive change, see [Figure 61](#).

Figure 61 C021 Glucose Values mg/dL (blue) with Corresponding Change from Baseline mg/dL (red), Visits 3 to 10, Minimum 7 Samples, 10030 Rows (entries), n= 1152 (49% of entries have positive change from baseline)



A subset of patients with extreme outlier low glucose values is selected for exploration of their profile of glucose values during the C021 study timeline. The threshold selected is 45mg/dL. There were 12 patients with a minimum glucose value during any of their study sample measurements that was ≤ 45 mg/dL, Table 72. The profile of individual glucose values for these patients is show in Figure 62 and Figure 63. This analysis reveals that the extreme low glucose values were sporadic and irregularly placed. They do not appear to represent a trend of sustained or incrementally worsening low glucose values.

Table 72 C021 Patients with at least 1 Post Baseline Glucose Value ≤ 45 mg/dL

#	Patients with glucose ≤ 45 mg/dL	Figure
1	YKP3089C021- (b) (6)	Figure 62
2	YKP3089C021- (b) (6)	Figure 62
3	YKP3089C021- (b) (6)	Figure 62
4	YKP3089C021- (b) (6)	Figure 62
5	YKP3089C021- (b) (6)	Figure 62
6	YKP3089C021- (b) (6)	Figure 62
7	YKP3089C021- (b) (6)	Figure 63
8	YKP3089C021- (b) (6)	Figure 63
9	YKP3089C021- (b) (6)	Figure 63
10	YKP3089C021- (b) (6)	Figure 63
11	YKP3089C021- (b) (6)	Figure 63
12	YKP3089C021- (b) (6)	Figure 63

Adverse events associated with low glucose:

The SOCs “endocrine disorders”, “investigations” and “Metabolism and nutrition disorders” are examined for preferred terms that may be associated with low glucose. This analysis revealed there were 2 entries for “hypoglycemia” and 2 entries for “type 2 diabetes mellitus” from 4 patients (one preferred term each). One of these 4 patients was also in the set of patients with any post baseline glucose value < 65mg/dL (n=162). There were also 26 patients with an entry of “weight decreased”. From among these 26 patients there were 3 that were also present in among the subject ID’s of patients with a glucose value < 65mg/dL. This exploration does not reveal notable overlap between patients with low glucose values and clinical events that may be associated with low glucose.

Figure 62 C021, Patients 1- 6 from Table 72, Glucose Values by Laboratory Day (LBDY), Visits 3-10

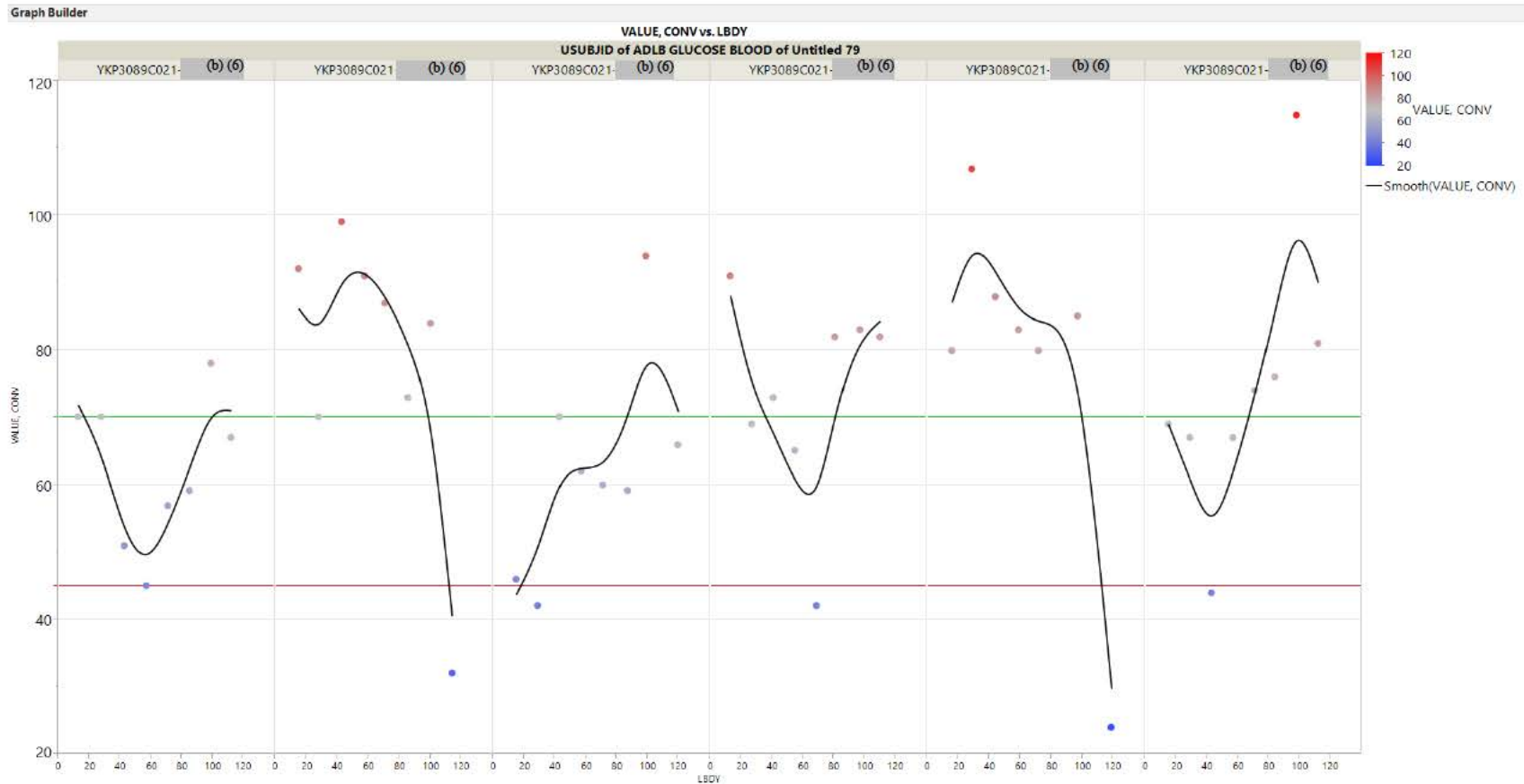
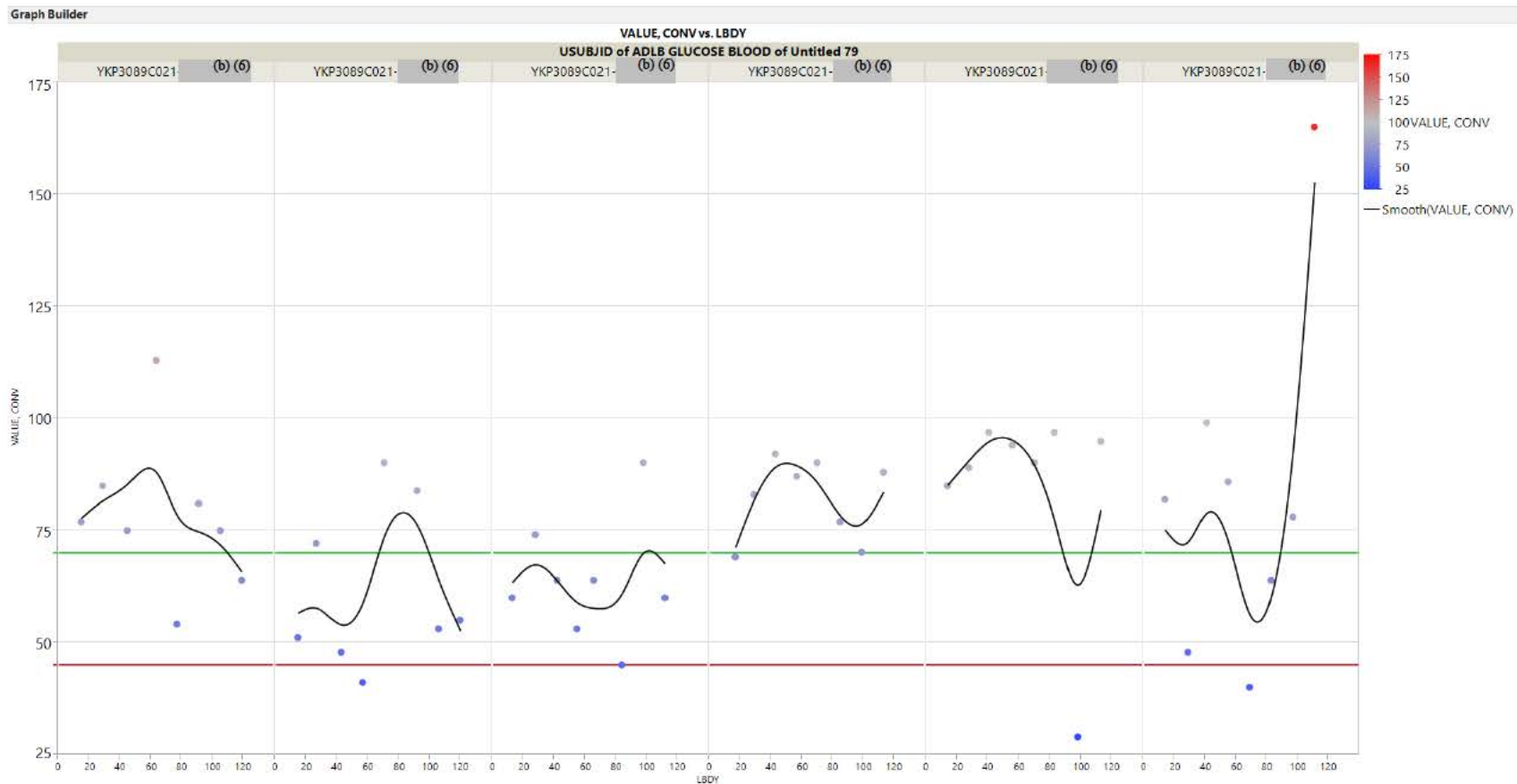


Figure 63 C021, Patients 7- 12, from Table 47, Glucose Values by Laboratory Day (LBDY), Visits 3-10



Reviewer Comment, glucose:

There is a higher frequency of post-baseline low glucose values than high glucose values although the assessment of change from baseline value reveals nearly equal frequency of increase and decrease from baseline when 86% of patients with participation in study C021 of 7 visits or more are examined. There is also a high frequency of critical low glucose values < 50mg/dL that occurred in 24 patients. When the most extreme outliers with values of ≤45mg/dL are examined, there is no consistent temporal relationship to the start of cenobamate treatment. There is also no trend of sequential decline in values over the study. This trend was not seen in controlled trial data. The clinical implication of these observations of low glucose laboratory measurements is uncertain.

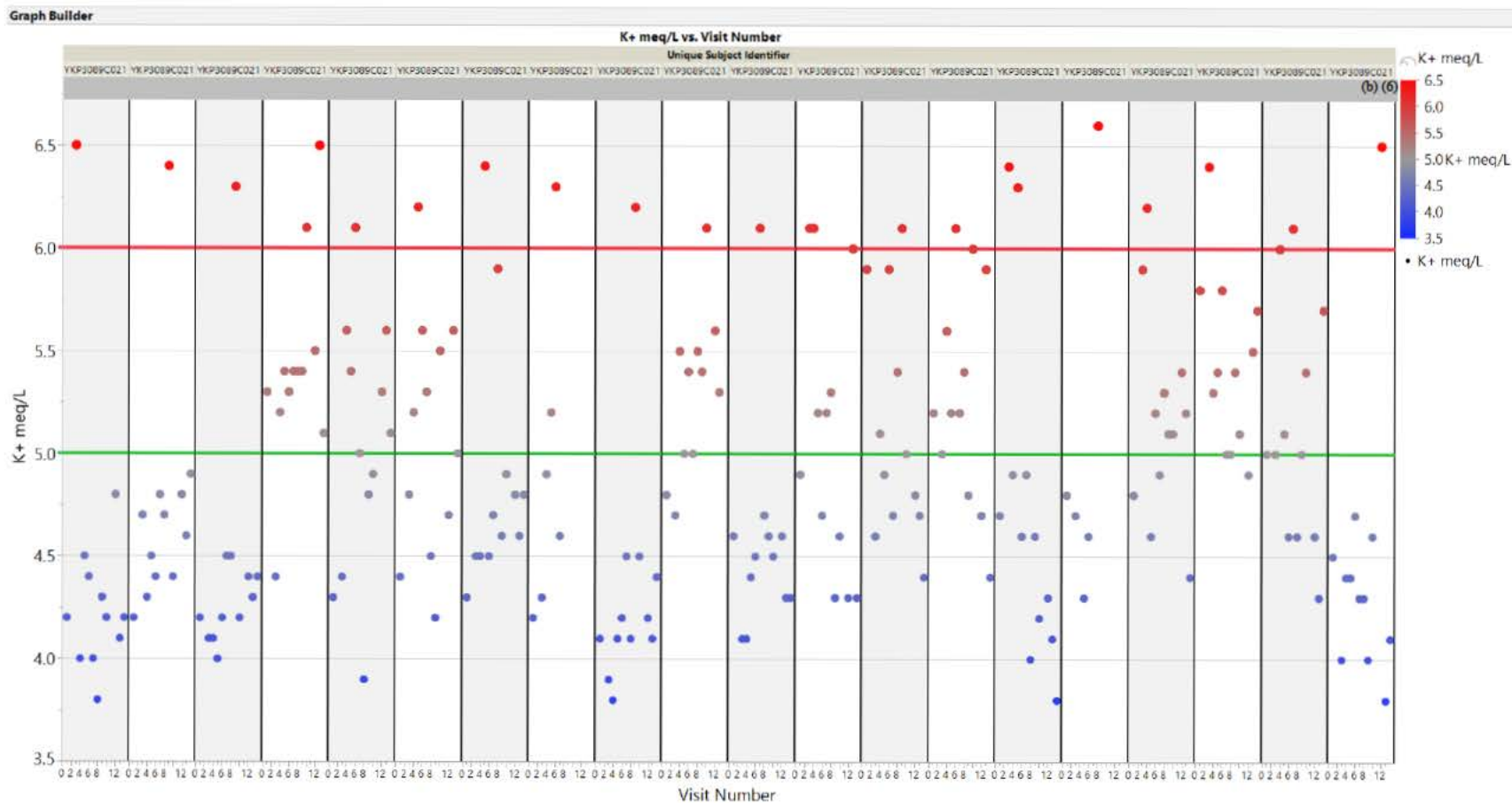
Potassium

>ULN:

The maximum post baseline potassium value for each patient was assessed. There were 391 (30%) patients with at least one OORR high potassium value that represented an increase over baseline. The most extreme outlier subset with potassium values >6meq/L were captured. There were 20 patients with at least one post baseline value >6meq/L that was also an increase over baseline. Four patients had baseline > ULN (5meq/L) with a maximum baseline of 5.9meq/L. Fifteen of the 20 patients had a single value > 6.0meq/L. In 7 of these 15 patients this single value greater than 6meq/L was the only OORR high value from baseline to visit 14. In eight patient there were no OORR high value except the isolated outliers greater than 6meq/L. In the remainder there were scattered instances of OORR high values less than 6meq/L. The distribution of potassium values among the 20 patients did not reveal a sequential escalation of potassium through study visits, see [Figure 64](#). The adverse events of these 20 patients are examined and reveals an entry for the preferred term “hypokalemia” from two patients and “Blood potassium increased” in a third. None was a serious adverse event although study drug was withdrawn in one patient due to “hepatic enzyme increased”. There were no cardiac adverse events identified.

Each patient has the mean of all post baseline potassium values computed. There were 29 (2.2%) patients with a mean of values OORR high that were an increase over baseline value.

Figure 64 C021, Potassium Extreme Outliers, 20 Patients with Value >6meq/L, Profile of Values at Visits 1(baseline)-14 by Patient ID



<LLN: The minimum post baseline potassium value for each patient was identified. From among these there were 27 (2%) patients with an OORR low value that represented a decline from baseline. There was a single patient with an OORR low value that was less than 3.0meq/L. This patient had an isolated low value of 2.8meq/L at study visit 4, day 24. All remaining values from baseline to study visit 14 were within reference range.

Each patient has the mean of all post baseline potassium values computed. There was 1 (.008%) patient with a mean of values OORR low mean value that was a decline from baseline.

Reviewer Comment, potassium:

During cenobamate treatment there is a consistent trend of potassium increase over baseline. There are also several extreme outliers with value > 6meq/L. there were no associated clinical adverse events except for an entry of hyperkalemia or blood potassium increased in 3 patients. These observations are in alignment with the trend to potassium elevation in the controlled trial safety data.

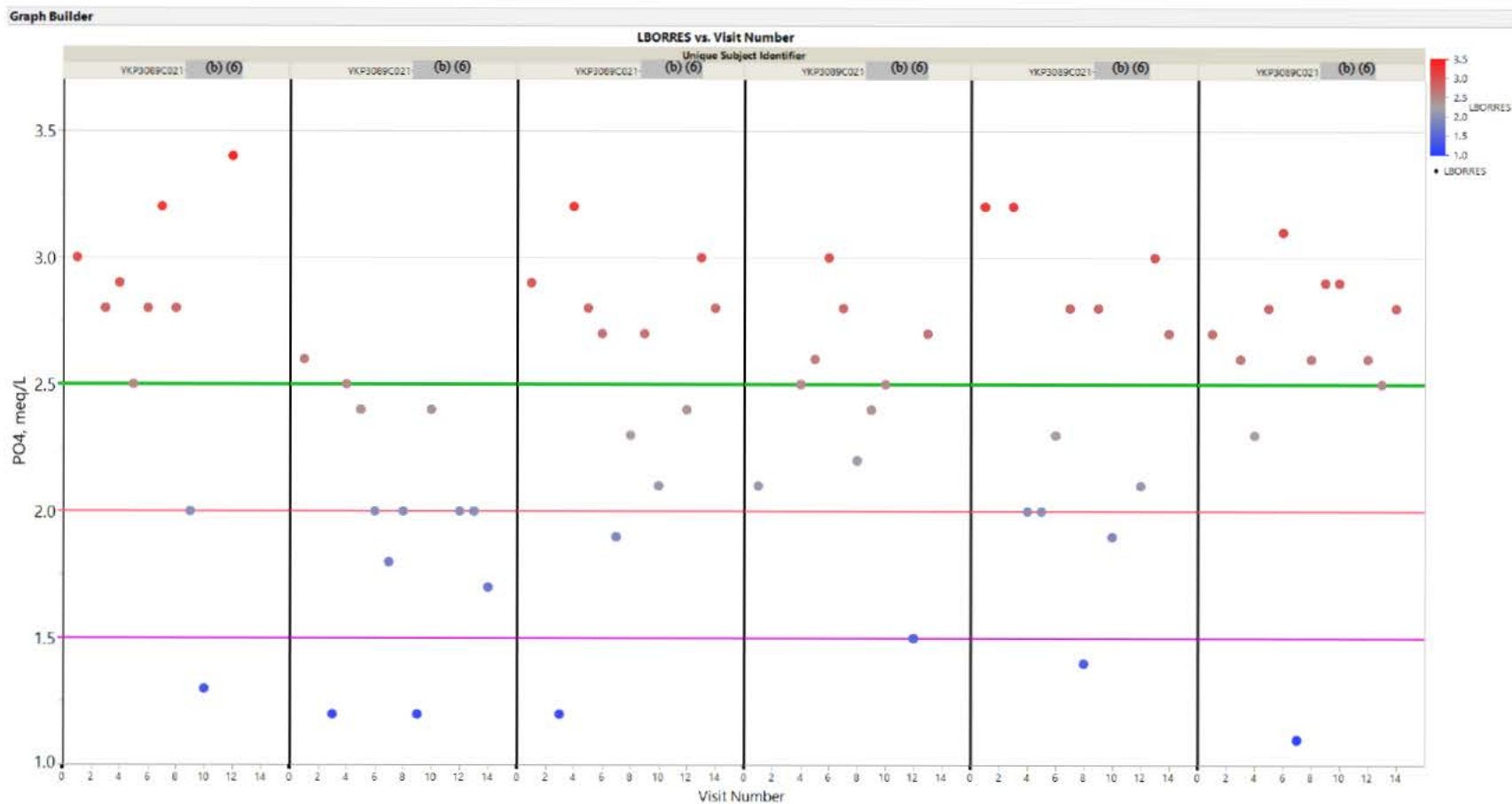
Phosphate

>ULN: There were 161 (12.2%) patients with at least one post baseline phosphate value that was OORR high that represented an increase over baseline. Within this group there were 3 patients had a phosphate value that was >2 x ULN. The profile of values across the study visits was examined for each patient. These phosphate values were single episodic elevations without associated adverse events.

<LLN: There were 267 (20.3%) patients with at least one post baseline phosphate value that was OORR low and was also a decline from the baseline value. There were also 40 patients with a post baseline phosphate < 2.0mg/dL. From among these patients there were 6 with a phosphate less than 1.5mg/dL. Baseline phosphate is examined, and it is found that 1.5% of patients have a baseline phosphate < 2.5mg/dL. It does not appear that low baseline values contribute to the trend toward low phosphate.

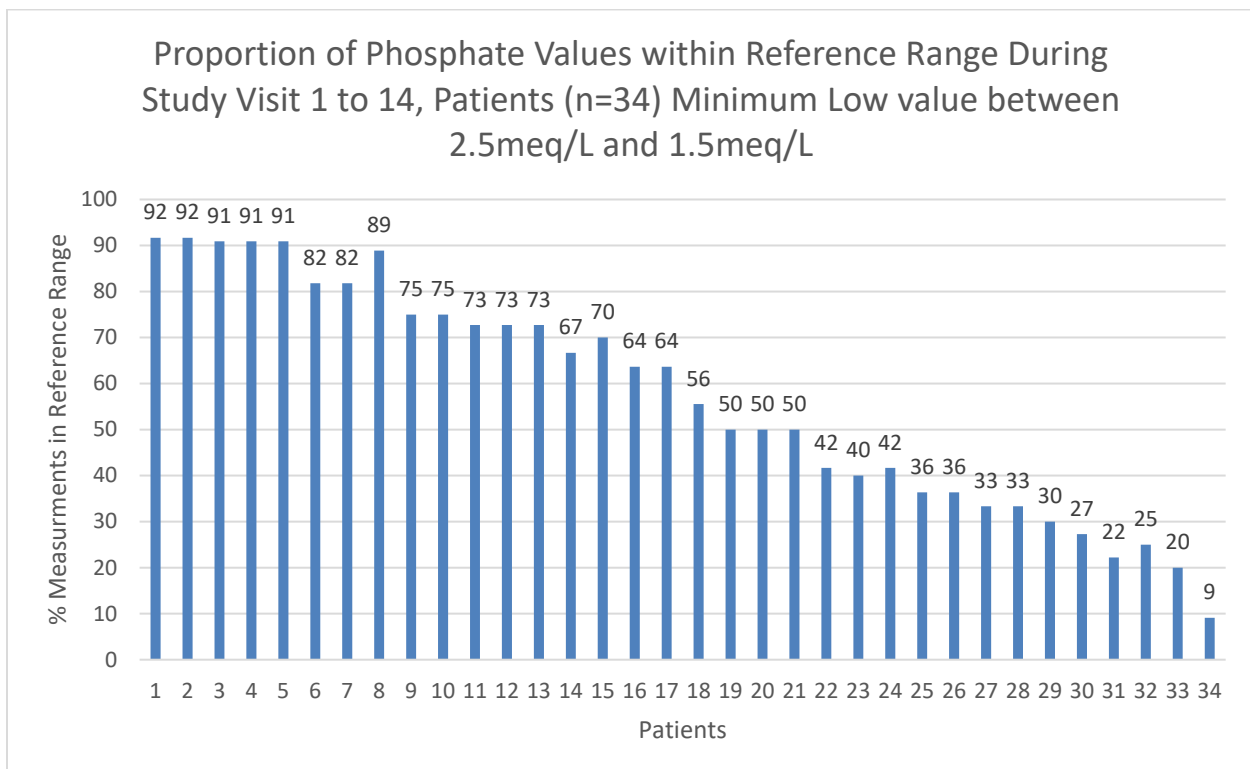
The phosphate levels over the course of the 1-year study of the 6 most extreme outlier instances identified from the 40 patients with phosphate <2meq/L identified in the paragraph above are examined. In four of the five patient the majority of phosphate values are within reference range. In the remaining patient only two of 12 measurements are within reference range. This same patient (YKP3089C021-(b) (6)) was the only patient that had two phosphate values < 1.5meq/L, see [Figure 65](#).

Figure 65 C021 Low Phosphate, Outliers with Minimum Value < 1.5meq/L (n=6), Distribution of Values by Study Visit



From among the remaining 34 patients with phosphate values < 2meq/L all values from measurements taken at visit 1 to 14 are examined to determine the proportion of OORR low values compared to values within reference range for each patient. This analysis reveals in 21 of 34 patients greater than half of phosphate values obtained over the course of the study are within reference range. The percent of values within reference range is shown in [Figure 66](#).

Figure 66 C021, Phosphate Measurements, Proportion of Phosphate Values within Reference Range During Study Visit 1 to 14 from 34 Patients OORR Low



The profile of adverse events from the 40 patients with phosphate < 2meq/L during study visits 1-12 are examined. Items of interest related to hypophosphatemia are CNS, Cardiac and Neuromuscular dysfunction. This examination revealed 158 adverse event entries from 92 preferred terms. There are no preferred terms from the SOC “cardiac disorders”. There are 45 entries in the SOC “nervous system disorders” from 17 preferred terms. The most frequent terms were “dizziness”, “somnolence”, and “headache”. There were two entries of “Paraesthesia” that may be seen in acute hypophosphatemia, overall the profile of “nervous system disorders” adverse events cannot be differentiated from the frequently occurring CNS events seen across the cenobamate treatment population.

Reviewer Comment, hypophosphatemia:

There was a notably higher frequency of minimum study value OORR low phosphate than OORR high phosphate with a proportion of 20.3% and 12.2% respectively. The frequency of extreme low outliers was also greater than extreme high outliers. The low values do not have a consistent temporal relationship to initiation of cenobamate treatment and do not manifest as a sequential declining trend. Examination of the adverse events from among the patients with any minimum value < 2meq/L does not reveal preferred terms clearly associated with hypophosphatemia, however, CNS dysfunction is frequent but is not easily differentiated from the trend of CNS dysfunction seen across cenobamate treatment. There does not appear to be a detectable clinical impact of the trend toward low phosphate. There were no critical values < 1meq/L.

Chemistry Reviewer Summary

Core issues of concern were present for the parameters ALT, Glucose, Potassium and hypophosphatemia. Detailed exploration of ALT revealed a notable excess of OORR high post baseline maximum values than OORR low post baseline minimum values. The frequency of maximum post baseline values greater than 3 x ULN was 1.7% (22 patients). There was a single notable case with elevation of ALT and bilirubin to Hy’s law levels, however this patient had a biliary tract obstructive lesion with resolution of the laboratory abnormalities post-surgery, [Figure 58](#). There were no Hy’s law cases. Examination of post baseline glucose value revealed a higher frequency of OORR low glucose values compared to OORR high. The ADAE dataset did not contain typical reference range limits so the boundaries for exploration were set as 65mg/dL to 150mg/dL by the reviewer. Although there were excess OORR low values observed the magnitude and frequency of change from baseline were similar. The low values were generally irregular and sporadic. There are no clear clinical implications of the sporadic post baseline OORR low observations. Examination of potassium values reveals a consistent trend of post baseline increase of potassium values with several extreme outliers. There were no concurrent adverse effects identified that may be related to hyperkalemia. The findings are in alignment with those seen for post baseline potassium values in the controlled dataset. An excess of low phosphate was also seen during the chemistry parameter review. There were no identifiable associated adverse effects and the OORR low values were generally irregular and sporadic in occurrence. The clinical implications of the low phosphate values are unclear. A

trend of decreasing globulin was also present but without identifiable association with adverse effects.

8.4.9. Vital Signs

Pool C013-C017 DB

Method of Analysis, the sponsor provides a categorical vital sign dataset as part of the ISS ADAE datasets. The categorical dataset is populated with present vital sign ranges as categories $\geq x$ value, $\leq x$ value for each patient meeting the boundaries for the given category. The frequencies by dose arm and category are generated by the reviewer for evaluation in [Table 73](#), [Table 74](#), [Table 75](#), and [Table 76](#) below.

Table 73 Pulse, Supine and Standing, Post Baseline by Frequency of Value, <60 bpm, >100 bpm and Arm

Measurement	ARM C013-C017	ARM (n)	# Patients	% Patients
Standing Pulse Rate, <60 bpm	Placebo	216	21	10
	100mg	108	7	6
	200mg	223	25	11
	400mg	111	11	10
Standing Pulse Rate, >100 bpm	Placebo	216	26	12
	100mg	108	16	15
	200mg	223	25	11
	400mg	111	8	7
Supine Pulse Rate, <60 bpm	Placebo	216	46	21
	100mg	108	28	26
	200mg	223	54	24
	400mg	111	29	26
Supine Pulse Rate, >100 bpm	Placebo	216	6	3
	100mg	108	2	2
	200mg	223	6	3
	400mg	111	2	2

Blood pressure

Table 74 Standing Diastolic Blood Pressure, Post Baseline by Frequency of Value, <90 mmHg, >140 mmHg, >160 mmHg and Arm

Measurement	ARM, C013-C017	n group	# Patients	% patient
Standing Systolic Blood Pressure, <90 mmHg	Placebo	216	4	1.9
	100mg	108	0	0.0
	200mg	223	7	3.1
	400mg	111	5	4.5
Standing Systolic Blood Pressure, >140 mmHg	Placebo	216	41	19.0
	100mg	108	21	19.4

Measurement	ARM, C013-C017	n group	# Patients	% patient
	200mg	223	33	14.8
	400mg	111	19	17.1
Standing Systolic Blood Pressure, >160 mmHg	Placebo	216	4	1.9
	100mg	108	2	1.9
	200mg	223	4	1.8
	400mg	111	1	0.9

Table 75 Standing Diastolic Blood Pressure, Post Baseline by Frequency of Value, <50 mmHg , >90 mmHg, >100 mmHg and Arm

measurement	ARM C013-C017	N Group	# Patients	% patients
Standing Diastolic Blood Pressure, <50 mmHg	Placebo	216	1	0.5
	100mg	108	1	0.9
	200mg	223	1	0.4
	400mg	111	2	1.8
Standing Diastolic Blood Pressure, >90 mmHg	Placebo	216	57	26.4
	100mg	108	24	22.2
	200mg	223	49	22.0
	400mg	111	23	20.7
Standing Diastolic Blood Pressure, >100 mmHg	Placebo	216	14	6.5
	100mg	108	6	5.6
	200mg	223	10	4.5
	400mg	111	4	3.6

Body Weight

Table 76 Body Weight, Baseline to End of Double-Blind Period, 7% Increase or Decrease by Arm and Frequency

Measurement	ARM C013-C017	ARM (n)	# Patients	% Patients
Body Weight, Decrease of >=7% from Baseline	Placebo	216	6	2.8
	100mg	108	2	1.9
	200mg	223	3	1.3
	400mg	111	7	6.3
Body Weight, Increase of >=7% from Baseline	Placebo	216	4	1.9
	100mg	108	8	7.4
	200mg	223	16	7.2
	400mg	111	10	9.0

Reviewer Comment, DB Vital Signs:

The frequency of post baseline standing pulse values in the range of bradycardia or tachycardia do not show substantiate change from placebo and there is not does relationship for the frequency in either category of <60 bpm or >100 bpm. Examination of supine pulse reveals an increased frequency in the <60 bpm category compared to standing but only a small differential from placebo at any dose and no dose response. Supine pulse >100 bpm has the lowest frequency, this is expected due to absence of maintaining vertical posture. In this range of pulse there is no difference between treatment and placebo, [Table 73](#).

The sponsor has provided a dataset with three categories of standing systolic blood pressure, [Table 74](#). The categories are <90mmHg, >140mmHg, and >160mmHg. In the category of post baseline standing systolic blood pressure < 90mmHg there are a low frequency of patients. there is a small differentiation from placebo and a dose response. This observation may be due to a small effect of orthostatic blood pressure challenge, but the clinical implications are not certain due to the low frequencies observed. There are a high frequency of patients with a standing systolic blood pressure value >140mmHg with no separation from placebo and no dose response. In the standing systolic blood pressure range > 160mmHg the frequencies are low in all arms with no separation from placebo and no dose response.

Standing diastolic pressure is also examined, [Table 75](#). In the range of diastolic pressure < 50mmHg the frequency was low with no dose response, the highest frequency (1.8%) was seen in the 400mg treatment arm at over 3 times the frequency in placebo. In the range of >90mmHg the highest frequency was in the placebo arm with no dose response seen in the cenobamate treatment arms although all had a lower frequency than placebo. In the range >100mmHg the frequency drops with the highest frequency in placebo and a dose response of declining frequency in the cenobamate treatment arms.

The trend seen in standing systolic and diastolic blood pressure is consistent with a trend of reduced value in the cenobamate treatment arms more prominent in the 400mg arm. Examination of the adverse event dataset reveals one episode of syncope in the 200mg treatment arm, there are no entries for blood pressure decreased and three entries for tachycardia with 0.4% in the 200mg treatment arm and 0.5% in the 400mg treatment arm. The small shift to higher frequencies in the lower blood pressure categories do not translate in to detection of a clinical signal in the adverse event profile of the DB adverse event dataset.

Body weight change is examined using the sponsors categorical vital signs dataset, frequencies by dose arm and weight change category are generated, [Table 76](#). Change in body weight from baseline to treatment is examined for frequencies of patients with an increase or decrease of $\geq 7\%$. The frequency of those patients with a decline in weight from baseline there was no difference between placebo and the 100mg or 200mg treatment arms. There was an increase frequency in the 400mg treatment arm over placebo by 3.5%. In the category of gain of $\geq 7\%$ there is an increase over placebo in all cenobamate treatment arms with the largest increase over placebo in the 400mg treatment arm. As a comparator, the weight trend in the placebo arm from baseline to end of treatment was examined. There was a mean gain of 3.7% across

213 patients with available measurements. In addition, one hundred eleven (111, 52%) patients had a weight gain while 94 (44%) patients had a weight loss and 8 (3.8%) had no change. This analysis reveals a small positive weight shift in placebo. Overall the weight gain trend in the cenobamate treatment arms does not reach the threshold for an adverse effect in section 6 of labeling.

C013-C017 OLE

Sponsor presentation

There were no clinically meaningful trends observed from baseline to any timepoint in vital sign parameters in both treatment groups¹⁶. Median changes from baseline were generally ≤ 4 mmHg for standing and supine systolic blood pressure and ≤ 2 mmHg for standing and supine diastolic blood pressure in both treatment groups. Median changes in standing and supine pulse rate were generally ≤ 4 bpm in both treatment groups.

In the LT OLE Pool, the majority of subjects in both treatment groups had a reported post-baseline supine and standing systolic blood pressure of >140 mmHg and diastolic blood pressure of >90 mmHg. In both treatment groups, more subjects who met the abnormal criteria had a post-baseline supine pulse rate of <60 bpm, respiratory rate of >20 breaths per minute, and temperature of <36.0 C.

The AEs potentially associated with changes in vital signs and include the following:

- Bradycardia: 1 (0.3%) subject in the cenobamate DB to OLE group had mild event.
- Pyrexia: 6 (1.8%) subjects in the cenobamate DB to OLE group and 2 (1.2%) subjects in the placebo DB to cenobamate OLE group. One (0.3%) subject in the cenobamate DB to OLE group had a severe event; all other events were considered as mild.
- Weight decreased: 13 (3.8%) subjects in the cenobamate DB to OLE group and 6 (3.7%) subjects in the placebo DB to cenobamate OLE group. One (0.3%) subject in the cenobamate DB to OLE group reported a severe event; all other events were considered as mild.
- Weight increased: 7 (2.1%) subjects in the cenobamate DB to OLE group and 3 (1.8%) subjects in the placebo DB to cenobamate OLE group. Two (0.4%) subjects had moderate events; all other events were considered as mild.
- Blood pressure decreased: 1 (0.3%) subject in the cenobamate DB to OLE group had a moderate event.
 - Blood pressure increased: 1 (0.3%) subject in the cenobamate DB to OLE group had a mild event.
- Body temperature increased: 1 (0.3%) subject in the cenobamate DB to OLE group had a moderate event.
- Syncope: 2 (0.6%) subjects in the cenobamate DB to OLE group and 1 (0.6%) subject in the

¹⁶ ISS, P137

placebo DB to cenobamate OLE group. One (0.3%) subject in the cenobamate DB to OLE group reported a mild event; all other events were considered as moderate.

- Presyncope: 2 (0.6%) subjects in the cenobamate DB to OLE group had mild events.
- Hypertension: 5 (1.5%) subjects in the cenobamate DB to OLE group and 6 (3.7%) subjects in the placebo DB to cenobamate OLE group. Three (0.6%) subjects had moderate events; all other events were considered as mild.
- Hypotension: 1 (0.3%) subject in the cenobamate DB to OLE group and 2 (1.2%) subjects in the placebo DB to cenobamate OLE group. A total of 2 (0.4%) subjects had mild events and 1 (0.2%) subject had a moderate event.

The following AEs potentially associated with changes in vital sign parameters were assessed to be treatment-related in the cenobamate DB to OLE group: weight decreased (11 [3.2%] subjects); weight increased (4 [1.2%] subjects); and bradycardia, blood pressure decreased, syncope, and hypotension (1 [0.3%] subject each). The following AEs potentially associated with changes in vital sign parameters were assessed to be treatment-related in the placebo DB to cenobamate OLE group: weight decreased (2 [1.2%] subjects), weight increased (1 [0.6%] subject), and syncope (1 [0.6%] subject).

In the placebo DB to cenobamate OLE group, the AE of hypotension in 1 (0.6%) subject was reported as serious, and the AE of weight decreased in 1 (0.6%) subject led to discontinuation of study drug.

Reviewer Comment, C013-C017 OLE:

The vital sign findings identified by the sponsor are in alignment with those from the reviewer examination of the double-blind phase of C013-C017 except for weight. There was a higher frequency of weight decrease than increase in the adverse event dataset. The signal for weight change is indeterminant.

C021

Sponsor Presentation

In general, changes in systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, weight, and height in each safety evaluable group were small and not clinically meaningful in Study C021¹⁷. Mean systolic and diastolic blood pressure and pulse rate remained lower than baseline values for most of the treatment period for all safety evaluable groups at each visit. At each visit, mean systolic blood pressure decreases were less than 3 mmHg and mean diastolic blood pressure decreases were less than 2 mmHg. Mean pulse rate decreases at each visit were less than 4 beats/min.

¹⁷ ISS P 138

Table 77 Study C021, Sponsor Table, Vital Signs. Patients with at Least 1 Post-Baseline Value Meeting Abnormal Criteria (ISS, P139- Table 59)¹⁸

Parameter Category	Cenobamate (N=1339)	Cenobamate and Phenytoin (N=83)	Cenobamate and Phenobarbital (N=37)	Cenobamate and Other AEDs (N=1219)
Systolic blood pressure				
<90 mmHg	41 (3.1)	2 (2.4)	1 (2.7)	38 (3.1)
>140 mmHg	279 (20.8)	21 (25.3)	13 (35.1)	245 (20.1)
>160 mmHg	36 (2.7)	4 (4.8)	0 (0.0)	32 (2.6)
Diastolic blood pressure				
<50 mmHg	28 (2.1)	0 (0.0)	2 (5.4)	26 (2.1)
>90 mmHg	267 (19.9)	21 (25.3)	10 (27.0)	236 (19.4)
>100 mmHg	49 (3.7)	5 (6.0)	1 (2.7)	43 (3.5)
Pulse rate				
<60 bpm	390 (29.1)	26 (31.3)	12 (32.4)	352 (28.9)
>100 bpm	53 (4.0)	1 (1.2)	0 (0.0)	52 (4.3)
Body weight				
Decrease of ≥7% from baseline	132 (9.9)	6 (7.2)	3 (8.1)	123 (10.1)
Increase of ≥7% from baseline	111 (8.3)	8 (9.6)	2 (5.4)	101 (8.3)
Respiratory rate				
<12 breaths/min	31 (2.3)	2 (2.4)	2 (5.4)	27 (2.2)
>20 breaths/min	242 (18.1)	22 (26.5)	6 (16.2)	214 (17.6)
Temperature				
>38.0°C	3 (0.2)	0 (0.0)	1 (2.7)	2 (0.2)
<36.0°C	376 (28.1)	31 (37.3)	12 (32.4)	333 (27.3)

Reviewer Comment: The vital sign SDTM VS dataset is examined for concordance with [Table 77](#). JMP clinical analysis tool is used to examine minimum and maximum shifts as well as mean post baseline values of visits 1-14 (1 year study visit).

Systolic Blood Pressure

<90mmHg

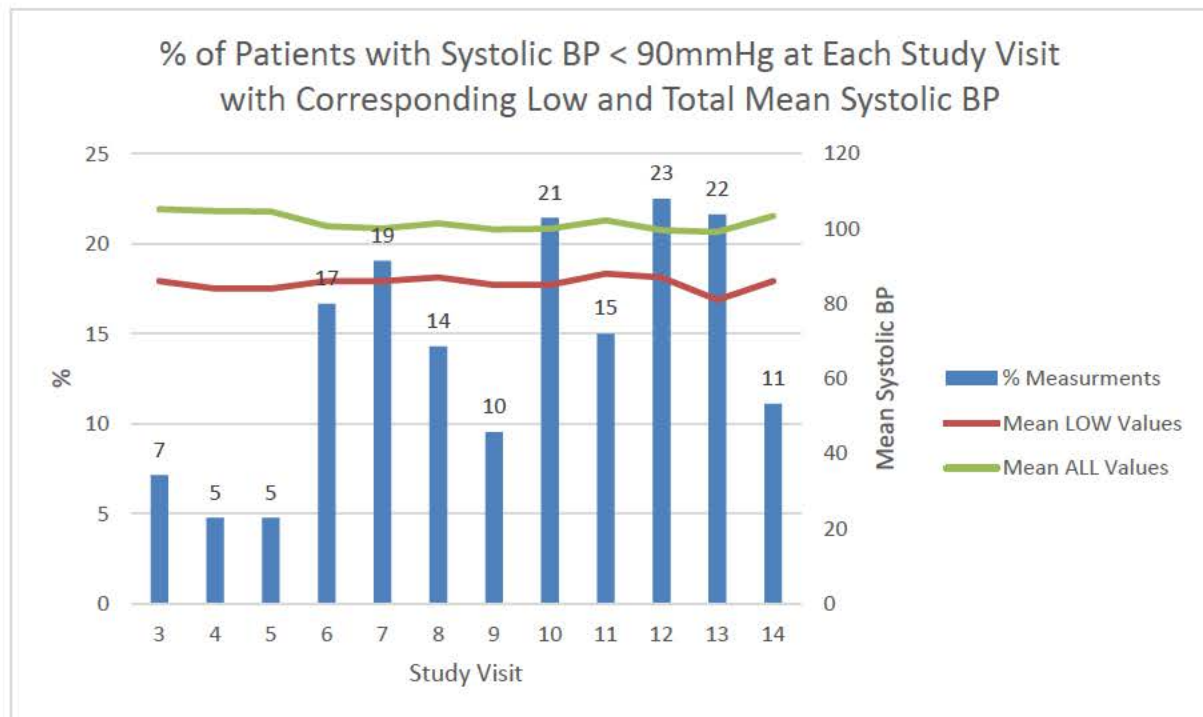
There were 42 (3.1%) patients identified with any post baseline systolic blood pressure <90mmHg. The profile of values from visit 3 to 14 is examined to assess the frequency of study measurements with a value less than 90mmHg. There were a total 489 of post baseline measurements from visit 3 to 14 (post baseline). From among these visits there were 422 (86%) measurements with values ≥90mmHg and 68 (14%) with values < 90mmHg. This indicates that a small proportion of values from these 42 patients were below 90mmHg during the course of the study. It is of interest to determine if there was a temporal relationship of the low value to

¹⁸ Vital sign measurements in study C021 are obtained after 5 minutes in the supine position

the start of cenobamate treatment and also how the proportion of low BP measurements (<90mmHg) was distributed across the study visits.

Examination of the distribution of the 42-patient subset, group measurements, by study visit is as granular as an individual patient by patient profile of each patient's blood pressure. Such an approach for a determination of whether a small number of patients had persistent sub 90mmHg value at each visit and reveals the magnitude of the individual values. However, the group distribution approach does provide an assurance that a majority of patients do not have a <90mmHg value at a large proportion of visits. Figure 67 reveals that the proportion of patients with a blood pressure decline <90mmHg increases at study visit 6 (mean study day 62) but does not exceed 23 percent of patients at any study visit. The lowest group mean blood pressure is seen at visit 13 (mean study day 272) when 37 of the initial 42 patients have measurements obtained. The profile of these systolic blood pressure outliers is consistent with the occurrence of sporadic elevations below 90mmHg. The group mean values of all measurements (*above and below the 90mmHg threshold*) are >100mmHg systolic pressure at all visits except number 13 where the mean is 99mmHg.

Figure 67 C021, Systolic BP: Patients with Any Post Baseline Value <90mmHG (n=42), Proportion of Measurements < 90mmHG at Each Study Visit with Corresponding Mean Systolic BP of All Measurements and Measurements Captured from below the 90mmHg Threshold by Visit.



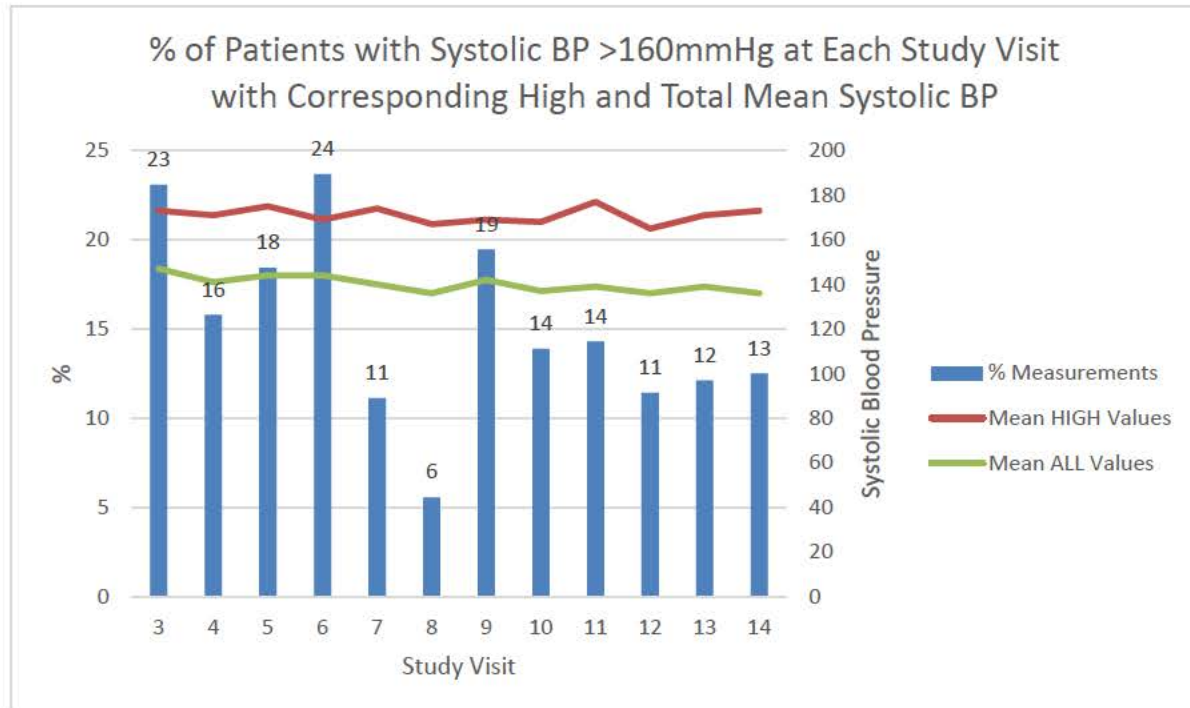
>160mmHg

There were 40 (3%) patients identified with a post baseline systolic blood pressure >160mmHg

that was an increase from baseline value (whether normal or high at baseline). Five of these patients had a systolic blood pressure that was greater than 160 at baseline. The top three outliers had a maximum systolic blood pressures during post baseline measurements of 194mmHg, 190mmHg, and 186mmHg respectively. These occurred at study visit number 3, 5 and 11, also respectively. These high values were sporadic with one other measurement > 160 among the three patients.

An assessment of the 40 patients with systolic blood pressure values >160 is performed to determine the proportion of values at each study visit that was > 160mmHg, the mean blood pressure of those measurements that were above the 160mmHg threshold at each visit and the mean of all measurements at each visits, [Figure 68](#). This analysis reveals the maximum proportion of measurements above the 160mmHg threshold is 24% at visit 6. The highest group mean value of the high blood pressure subset occurs at visit 11 with a value of 177. Thereafter the group mean of high values remains steady with a range from 168mmHg to 177mmHg. The mean of all values has a maximum at visit 3 with a value of 147, thereafter the means trend lower to a minimum of 136mmHg at visit 14. The profile of these systolic blood pressure outlier is consistent with sporadic elevations above 160mmHg with group mean values that are in the range of CTCAE Grade 1 and Grade 2.

Figure 68 C021, Systolic BP: Patients with Any Post Baseline Value >160mmHg (n=40), Proportion of Measurements >160mmHg at Each Study Visit with Corresponding Mean Systolic BP of All Measurements and Measurements Captured from Above the 160mmHg Threshold by Visit.



Reviewer Comment, Blood pressure:

The profile of outlier patients with systolic blood pressure values <90mmHg or >160mmHg show these events are primarily due to sporadic elevations and they occur in small subsets, approximately 3% of patients in the high and low outlier groups. This analysis does not reveal a signal for widespread sustained depression or elevation of blood pressure.

Weight

An outlier (YKP3089C021- (b) (6)) is identified with an increase of weight from 60.8 kg, day 30, to 141.3kg, day 217, in 187 days. This would equal a daily weight gain in that interval of 0.43kg (.95lbs). The weight then drops to 66.4kg by day 372 (155 days). This equals a decline of 0.48kg /day. The plausibility of this weight gain and loss profile is uncertain. The patient has an adverse event of “depressed mood”. This patient is excluded from the remainder of the study group analysis.

The proportion of patients with a maximum post baseline weight increase of $\geq 7\%$ or have a decline $\leq 7\%$ are captured. There were 118 (9.3%) patients that had an increase of $\geq 7\%$ while there were 172 (13.6%) patients with a post baseline decline that was greater than or equal to 7%.

In the group with $\geq 7\%$ weight loss there were 48 (3.8%, n=1262) patients with a loss of more than 10kg (22lbs). The group mean weight loss of the 172 patients was -14.7kg with a median of -12.7 kg and a maximum loss of -37kg. The cohort with a $\geq 7\%$ weight gain there were 17 (1.3%, n=1262) patients with greater than 10kg weight gain and the subset of 118 patients with an increase of $\geq 7\%$ had a mean and median weight gain of 7.5kg and 6.5kg respectively with a maximum of 26kg (with above outlier excluded).

Reviewer Comment, weight:

There is an excess of weight loss over weight gain in the open label safety study that is divergent from the small excess of weigh gain over weight loss seen in the controlled study data. The frequency and magnitude of weight loss over weight gain in this one year open label study reveal a potential signal for weight loss.

Reviewer Summary, Vital Signs: examination of pulse reveals an excess of supine pulse > 60 bpm over a pulse > 100 bpm. This is not divergent from expectations for supine resting pulse in a population with a mean age of 40 years old. Systolic blood pressure does not reveal a clinically meaningful signal for depression or elevation of blood pressure. There is a potential signal for weight loss, but this does not reach a threshold of likelihood the observations diverge from the background variability.

8.4.10. Electrocardiograms (ECGs)

Study C013

Heart Rate

Examination of mean heart rate across study visits from baseline (visit 3) to visit 12 reveals a small mean decline of 2.31 bpm in the cenobamate treatment arm (200mg) compared to 0.93 bpm in the placebo arm. Examination of the frequency of minimum change from baseline (largest negative change) of ≤ -20 bpm reveals there were 13 patients in the cenobamate group that had a decrease in heart rate of ≥ 20 bpm with a group mean decline of these thirteen patients was -28 bpm. In the placebo arm there were 11 patients that met the decline of 20 or more bpm with a group mean of -22 bpm. Examination of the frequency of maximum post baseline change in heart rate > 20 bpm reveals there were 10 patients in the cenobamate treatment arm and 5 in the placebo arm that met this threshold with mean increase within this group of 24 bpm in each treatment arm. [The is an excess of post baseline decline in heart rate \$< -20\$ bpm compared to increase in heart rate \$> 20\$ bpm.](#)

PR Interval

There was a mean increase in PR interval from visit 3 to visit 12 of 1.88msec in the cenobamate treatment arm while in the placebo arm there was an increase of 1.34msec. Examination of the frequency of patients with a normal baseline to any post baseline greater than 200ms reveals there were 5 patients in the cenobamate treatment arm and 4 in the placebo treatment arm

that met this condition. The cenobamate mean and median post baseline values for this subset (5 patients) in the cenobamate treatment group were 211 and 205 respectively. The mean and median values in the 4-patient post baseline placebo subset were 209 and 210 respectively.

[There is no substantive difference in the upshift in PR interval between the placebo and cenobamate treatment arms.](#)

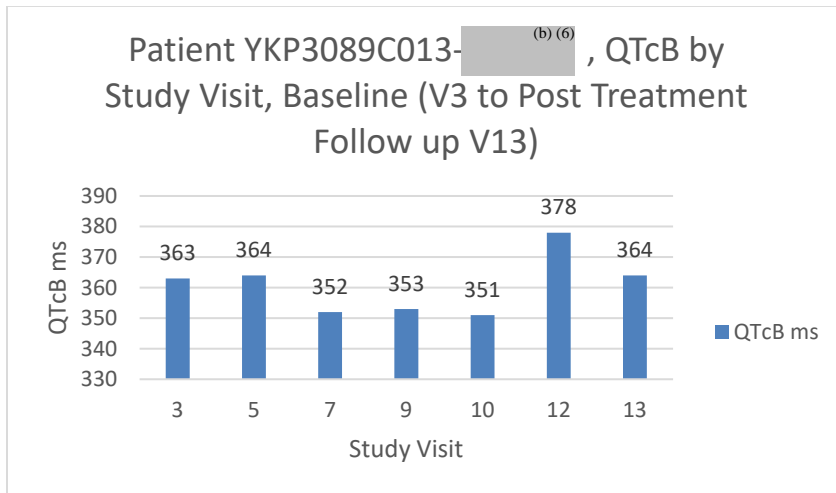
QTcB

Examination of mean and median QTcB from Visit 3 to Visit 12 reveals a mean decrease of -4.6ms in the cenobamate treatment arm compared with a decrease of -1.3 ms in the placebo arm. The median change from V3 to V12 in the cenobamate arm was -4ms compared to -1ms in the placebo treatment arm.

Examination of the frequency of an increase in QTcB in the post baseline interval that were ≥ 30 ms reveal there were 21 patients in the cenobamate treatment arm and 19 patients in the placebo arm that met this criteria. The mean and median increase from baseline for this subset in the cenobamate treatment arms were 38ms and 35ms respectively while the mean and median increase over baseline for the placebo subset were 38ms and 34ms respectively. Examination of the maximum declines (QTcB) from baseline that were ≤ 30 ms reveal there were 26 (23.%) patients in the cenobamate treatment arm and 17 (15.6%) patients in the placebo arm that met this criteria. The mean and median values for this cenobamate treatment arm subset were -41ms and -36.5ms respectively while the mean and median for the placebo group were -39ms and -35ms respectively.

Examination of the frequency of shift from normal baseline to a QTcB < 360ms reveals there were 3 patients in the cenobamate treatment arm and 5 patients in the placebo arm that met this condition. The mean and median QTcB for the cenobamate arm were 352ms and 351ms respectively while the mean and median of the placebo arm were 352 and 353 respectively. From among the three patients in the cenobamate treatment arm with a post baseline decline to <360ms the most sustained decline occurred in patient YKP3089C013-(b) (6) [Figure 69](#).

Figure 69 C013 Patient YKP3089C013- (b) (6) , QTcB



Reviewer Comment QTcB: There is negative mean change in QTcB that is greater in the cenobamate treatment arm than in the placebo arm. There is also an excess of patients in the cenobamate arm compared the placebo arm with a decline in QTcB that exceeds -30ms. There is a signal for a decline in QTcB associated with cenobamate treatment.

Summary: there is a small signal for decline in heart rate and QTcB associated with cenobamate treatment.

Study C017

Heart Rate

Mean change in heart rate is examined across the treatment arms between study visits V3 (day 1 baseline) and V9 (End of treatment day 127). The mean change in heart rates across the treatment arms were +1, 0, -2.2 and -2.1 in the placebo, 100mg, 200mg and 400mg treatment arms respectively. The median change in heart rates were +3, 0, -2, and -1 in the placebo, 100mg, 200mg and 400mg treatment arms respectively.

The frequency of heart rate change in the post baseline interval that was ≥ 20 bpm is examined across the treatment arms. There were 9, 7, 4, and 3 patient each in the placebo, 100mg, 200mg and 400mg treatment arms with a ≥ 20 bpm increase over baseline. The mean change from baseline in the increased pulse subsets were 23, 24, 22 and 27 bpm in the placebo, 100mg, 200mg and 400mg treatment arms respectively while the median changes were 21, 24, 22, and 26 bpm respectively.

Examination of the declines in heart rate at across the study visits and treatment arms reveals there were 6,6, 9, and 6 patients in the placebo, 100mg, 200mg and 400mg arms respectively with a post baseline decline < -20 . The mean change for each of these (20bpm decline) subsets

were -24, -28, -25, and -28 bpm in the placebo, 100mg, 200mg, and 400mg treatment arms respectively.

PR Interval

Examination of the change in mean PR interval between baseline V3 and end of treatment interval, V9 reveals the change in mean values for the placebo, 100mg, 200mg and 400mg treatment arms were 1.3, -1, 0.8, and -0.7ms respectively.

The frequency of post baseline increase in PR interval ≥ 30 ms was examined across treatment arms. There were 4, 9, 3, and 3 patients each in the placebo, 100mg, 200mg and 400mg treatment arms respectively with a post baseline maximum increase in PR interval of 30ms or greater. The frequency of post baseline decrease in PR interval ≤ -30 ms was next examined. There were 2, 2, 3, and 8 patients in the placebo, 100mg, 200mg and 400mg treatment arms with a decline in PR interval ≥ 30 ms. The mean decline in these subsets by arm were -42, -37, -37, and -37ms respectively.

Examination of the frequency of post baseline PR interval greater than 200ms or less than 120ms where baseline was within normal limits reveals no substantive difference between the placebo and all treatment arm values. There is also no dose response in the frequency of OORR (120 to 200ms) high and low post baseline values.

Table 78 C017, PR Interval, Patients with Post Baseline Values <120ms or >200ms by Treatment Arm with Group Mean PR interval of Subset, From Normal Baseline

Treatment arm	# Pts < 120	% Pts	Group Mean < 120ms	# Pts >200ms	% Pts	Group Mean > 200ms
P	4	3.8	113	5	4.8	208
YKP3089 100	2	1.9	119	6	5.6	204
YKP3089 200	3	2.7	118	7	6.4	208
YKP3089 400	6	5.4	117	5	4.5	210

QTcB

The mean and median QTcB change from baseline to Visit 9 (day 127) are examined by treatment arm. This analysis reveals a dose related decline in QTcB where the placebo mean change from baseline is -1.3ms and the 100mg, 200mg and 400mg mean change from baseline are -1.8ms, -3.6ms, and -6.1ms respectively. The median change from baseline for all treatment arms are 0, -2ms, -3ms, and -4.5ms in the placebo, 100mg, 200mg and 400mg treatment arms respectively.

Examination of the frequency of patients with an increase in QTcB in the post baseline interval that were ≥ 30 ms reveal the distribution was 6, 15, 12, and 7 patients that met the condition in the placebo, 100mg, 200mg and 400mg treatment arms respectively. The mean increase in QTcB of those in the subsets ≥ 30 ms were 37ms, 40ms, 39ms, and 43ms respectively.

Examination of the frequency of patients with a decline in QTcB in the post baseline interval

that was ≤ -30 ms reveal the distribution was 11, 12, 16, and 20 in the placebo, 100mg, 200mg and 400mg treatment arm respectively. The corresponding group mean change in these less than 30ms subgroups were -41ms, -43ms, -39ms, and -43ms in the placebo, 100mg, 200mg and 400mg arm respectively, [Table 79](#).

Table 79 C017, QTcB, Frequency of Change from Baseline >30ms or <30ms with Group Mean by Treatment Arm

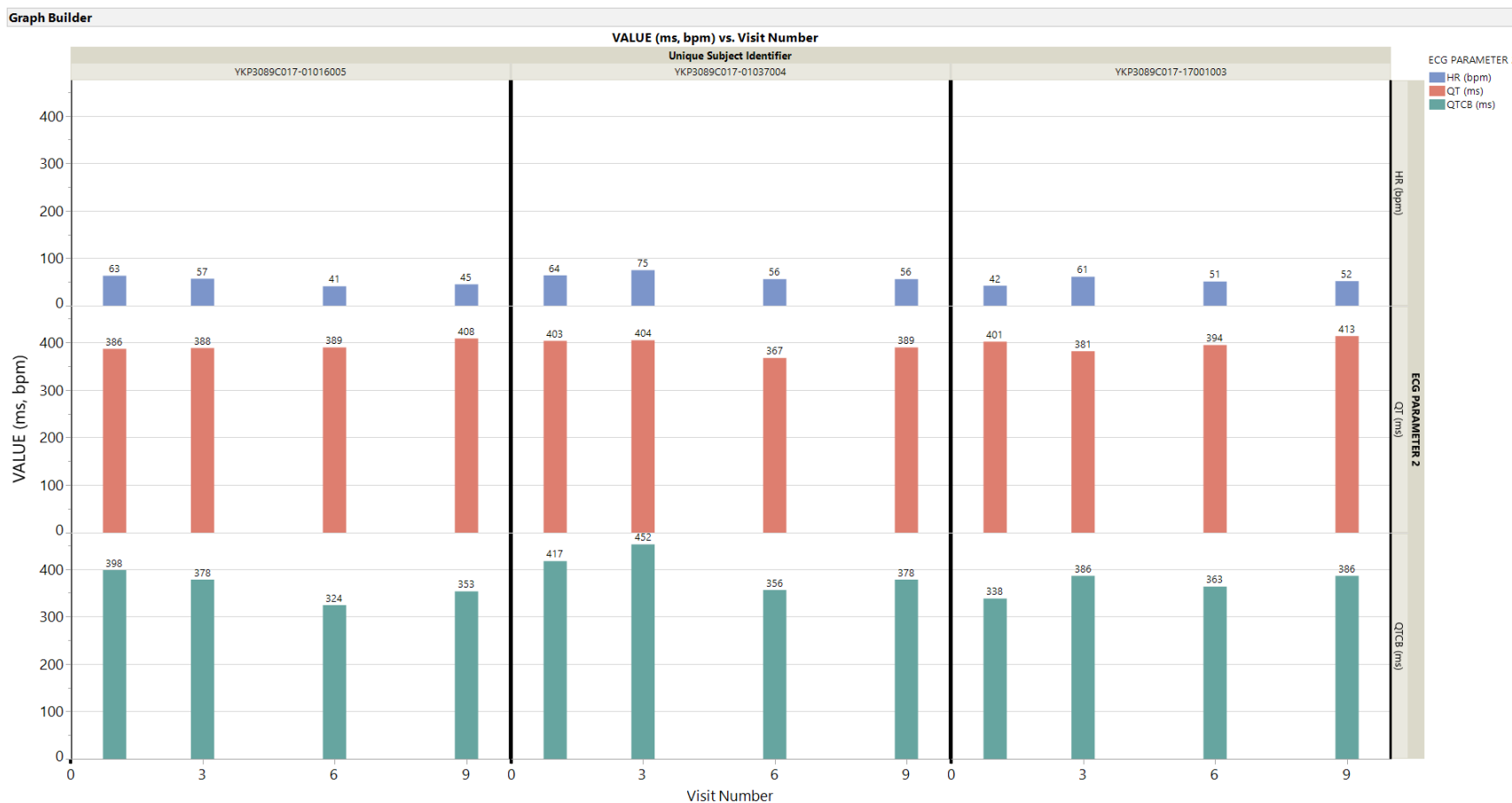
ARM	# Pts PB > 30ms increase	# Pts	Mean CHG from BASE, > 30ms group	# Pts < -30ms decline	# Pts PB < 30ms decrease	Mean CHG from BASE, < 30ms group
Placebo	6	5.7	37	11	10.5	-41
YKP3089 100	15	13.9	40	12	11.1	-43
YKP3089 200	12	10.9	39	16	14.5	-39
YKP3089 400	7	6.3	43	20	18.0	-43

Examination of the frequency of patients that have post baseline QTcB values reveals there were 4, 5, 5, and 3 patients in the placebo, 100mg, 200mg, and 400mg treatment arms that had a QTcB of < 360ms. The subset group mean values were 351, 355, 348 and 339 in the placebo, 100mg, 200mg and 400mg treatment arms respectively, [Table 80](#). The individual QTcB values for all study measurements are examined from the three patients in the 400mg treatment arm with QTcB <360ms and group mean QTcB of 339ms. This evaluation reveals that patient YKP3089C017-(b) (6) has a QTcB of 324ms on study visit 6 when corresponding heart rate was 41 bpm. Uncorrected QT was 386ms. In all three patients the uncorrected QT was > 360ms while the low QTcB values corresponded to low heart rates, [Figure 70](#).

Table 80 C017, Patients with normal Baseline and Post Baseline QTcB Value < 360ms with Mean of Group

Arm	# Patients	% Pts < 360 PB	Mean(QTcB TrialMin)
Placebo	4	3.8	351
YKP3089 100	5	4.6	355
YKP3089 200	5	4.5	348
YKP3089 400	3	2.7	339

Figure 70 C017, Outlier Low, QTcB <360ms, Patients YKP3089C017- (b) (6), YKP3089C017- (b) (6), YKP3089C017- (b) (6) by Study Visit and QT, QTcB, Heart Rate,



Reviewer Comment: In the evaluation of study C017 there was no substantive difference in pulse trend between cenobamate and placebo treatment arms. There was a signal for a decline in QTcB that was evident in a dose related decline in group mean values and a dose related excess of declines < 30ms. The most severe outliers' declines were examined, in one case a QTcB of 324ms was

associated with an outlier low heart rate of 41 bpm. The adverse event profile of all patients with a post baseline QTcB < 360ms was examined, there was one event in the “Cardiac Disorders” SOC, this event was the preferred term “sinus bradycardia” in one patient. There was one preferred term of note from the “nervous system disorders” SOC. This was the term “Loss of consciousness” in two patients age 31 and 24 years, subject ID’s YKP3089C017- (b) (6), YKP3089C017- (b) (6) in the 100mg and 200mg treatment arms respectively. These events occurred in the double-blind treatment interval on study days 30 and 108.

C013-C017 ECG Summary: In the controlled study data there was a signal for decline in heart rate noted in study C013 that was not observed in study C017. In both studies there was a signal for decline in QTcB while in study C017 there was a dose related association.

8.4.11. QT

A thorough QT study was performed by the sponsor and evaluated by the IRT for QT studies. The summary from the final consult document is provided below. This study reveals that cenobamate shortened the QTc interval in a dose dependent manner with a mean reduction of -9ms at the 200mg dose and -16ms for a 500mg dose (one in a day). The IRT has also recommended post marketing non-clinical study to determine the anti-arrhythmic class (Na⁺ channel blockade) of cenobamate to better understand potential risk, as noted in the summary below.

“Summary

Cenobamate shortened the QTc interval in a dose-dependent manner — the largest mean reduction in QTc was -9 ms for 200 mg QD and -16 ms for 500 mg QD. A decrease from baseline of more than 20 ms was observed in 31% subjects taking 200 mg and 66% taking 500 mg compared to 7-17% for placebo. There were 4% subjects taking 200 mg QD and 8% subjects taking 500 mg QD with QTc <350 ms. The magnitude of QTc shortening is similar to BANZEL (rufinamide), another anti-epileptic drug, which carries a warning for QT shortening and we therefore recommend inclusion of a similar warning in the label for cenobamate. The shortening of the QTc interval is likely due to inhibition of the cardiac sodium channel, which raises potential safety concerns with its use in patients with structural heart disease and its potential to unmask Brugada syndrome. Therefore, we are recommending additional nonclinical studies to understand the type of sodium channel blockade (see our recommendation in section 2.1).

The effect of cenobamate was evaluated in Study YKP3089C020. The highest dose that was evaluated was 500 mg QD, which covers the therapeutic exposures with the highest clinical dose (400 mg QD). The data from Study YKP3089C020 was analyzed using central tendency as the primary analysis (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (Appendix 5), exposure-

response analysis (section 4.5), and categorical analysis (section 4.4).

Table 81 The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
QTcF	Cenobamate 200 mg QD (day 35)	0.5h	-8.6	(-12.3, -5)
QTcF	Cenobamate 500 mg QD (day 63)	0.5h	-16.0	(-19.8, -12.3)

The observed, geometric mean of steady state C_{max} at 200 mg QD and 500 mg QD dose levels are 23.1 ug/mL and 63.8 ug/mL, respectively. This is generally in alignment with previous observations at the same dose levels. According to the sponsor's conclusion on dose proportional increase in C_{max,ss} (summary of clinical pharmacology), the 500 mg QD dose (i.e., the maximum tolerated dose in healthy subjects) in this TQT study provided approximately 1.25-fold exposure margin for the maximum therapeutic dose (i.e., 400 mg QD). There are no known intrinsic or extrinsic factors (i.e., sex, age, race, food, mild to severe renal impairment, or mild to moderate hepatic impairment) that substantially increase cenobamate exposures. The effect of severe hepatic impairment on cenobamate exposure has not been evaluated and the proposed label does not recommend its use in these patients."

8.4.12. Immunogenicity

N/A Cenobamate is a small molecule

8.5. Phase 1 Safety

Table 82 Phase 1 Study Overview, Dosing, Design, Objective, Maximum Cenobamate Dose, Sample Size, Post Cenobamate Treatment Day.

STUDYID	dosing	Design	purpose	peak dose	Study Duration	n -PBO	n- YKP	post YKP Study day (*, *= washout)	YKP Treatment Duration
AA22780	single dose (SAD)		PK	750	1	33	77	2	1
AA24143	MAD		PK	200	17	15	35	14	14
AA39450	single dose	Crossover	BE food	300	22	0	16	2, 22	1
AA40616	single dose		photosensitivity	400	3	0	12	2	1
AA41857	single dose (SAD)		mass balance	400	1	0	6	2	1
YKP3089C006	multiple dose, 1/pd	1 sequence, 3 Period	PK-contraceptive	100	35		28	35	30
YKP3089C009	MAD		PK 250-300mg	300	17	6	14	18	17
YKP3089C010	PK	1 sequence, 3 Period	PK DDI YKP-VPA	150	19		16	26	20
YKP3089C011	PK	1 sequence, 3 Period	DDI, YKP-CBZ	200	25		16	40	25
YKP3089C014	PK	1 sequence, 2 Period	DDI, YKP-CBZ-Metab	200	42		16	43	14
YKP3089C016	PK	1 sequence, 4 period	DDI, YKP-PHT	200	69		16	70	28
YKP3089C018	MAD	3 sequence, 4 period	PK titration	600	29	9	21	30	29
YKP3089C019	single dose	1 sequence, 2 period	BE Tablet	100	28		14	2	1
YKP3089C020	multiple	3 sequence, 3 Period	TQT	500	65	54	52	66	64
YKP3089C022	50mg-200mg, step 50	1 sequence, 2 Period	DDD, YKP-PB	200	62		16	56	35
YKP3089C024	single dose 200mg and 400mg YKP to compare to alprazolam with 16 day washout	10 sequence, 5 way	abuse potential	400				2, 17	1
YKP3089C026	multiple	1 sequence	DDI, P450 probe	200	109	0	24	110	98
YKP3089C027	Single dose		hepatic impairment	200	6		24	2	1
YKP3089C028	single dose		renal impairment	200	6		31	2	1
YKP3089C029	single dose (SAD)	4-way crossover	ETOH interaction	200	63		30	0	
YKP3089C030	single dose		Age Effect on PK	200	12	0	26	2	1

Entries from the Phase 1 ISS are examined. In the set with SAFFL 1 and SAFFL 2 affirmative there were examined. There were 2006 adverse event entries from 328 patients from 20 studies (Table 82), under 311 preferred terms.

Death

There was a death in study YKP3089C020 the TQT study. Patient YKP3089C020- (b) (6) developed an eosinophilic myocarditis due to DRESS and had a fatal outcome. This case is entered in Section 8.4.1 and Submission Specific Safety Issues, Section 8.6.1, [DRESS Risk](#).

Serious Adverse Event (SAE)

There were 10 serious adverse event entries from 8 patients. Two entries were from patient YKP3089C020- (b) (6) who had a fatal outcome, identified above. The preferred terms entered were “Drug reaction with eosinophilia and systemic symptoms” and “Eosinophilic myocarditis”.

There were two serious adverse events related to hypersensitivity, one a fatal DRESS case, the second entered as an SAE of Nausea but on examination of the narrative report the event occurred in the context of a serious hypersensitivity reaction. A third serious adverse event of hypersensitivity occurred in phase 1 not entered as an SAE but resulted in discontinuation. These three cases are presented in greater detail in section 8.6.1 [DRESS Risk](#). T One patient had features of marked central nervous system intoxication with a fall and head injury. A spontaneous abortion occurred in the latter phase of an alcohol interaction study and a 71-year-old patient had an episode of hypertension after a single dose of cenobamate in a PK study, see [Table 83](#)

Table 83 Phase 1 Serious Adverse Events

USUBJID	AGE	SEX	Dose	Study Day	Study Date	Preferred term	Comment																		
YKP3089C016- (b) (6)	19	F	300	20	(b) (6)	Nausea (<i>hypersensitivity</i>)	25 additional TEAE entries Hypersensitivity Rxn, no related PT																		
YKP3089C018- (b) (6)	50	M	400	14	(b) (6)	DRESS	<table border="1"> <thead> <tr> <th colspan="3">YKP3089C018- (b) (6) : SAE, DRESS dose and onset</th> </tr> <tr> <th>Study Day</th> <th>Dose</th> <th>Comment</th> </tr> </thead> <tbody> <tr> <td>1-5</td> <td>200</td> <td></td> </tr> <tr> <td>6-10</td> <td>300</td> <td></td> </tr> <tr> <td>11-15</td> <td>400</td> <td>DRESS Onset Day 14</td> </tr> <tr> <td>16-22</td> <td>500</td> <td></td> </tr> </tbody> </table>	YKP3089C018- (b) (6) : SAE, DRESS dose and onset			Study Day	Dose	Comment	1-5	200		6-10	300		11-15	400	DRESS Onset Day 14	16-22	500	
YKP3089C018- (b) (6) : SAE, DRESS dose and onset																									
Study Day	Dose	Comment																							
1-5	200																								
6-10	300																								
11-15	400	DRESS Onset Day 14																							
16-22	500																								
YKP3089C020- (b) (6)	38	F			(b) (6)	DRESS	Fatal- see above																		
YKP3089C018- (b) (6)	41	M	400	25	(b) (6)	Head injury	Fall at study site, features of intoxication- bumping into walls, losing balance, wobbly gait, feeling drunk, slurring words. 16 additional TEAE entries)																		
YKP3089C018- (b) (6)	41	M	400	25	(b) (6)	Mental status changes																			
YKP3089C024- (b) (6)	27	M		148	(b) (6)	Gunshot wound	The subject was hospitalized, and no other information was available. On (b) (6), the mother of the subject notified the site that the subject was discharged on that date. The site believed the subject to be incarcerated and was unable to contact the subject.																		
YKP3089C024- (b) (6)	19	M		102	(b) (6)	Gunshot wound	Medical records confirmed gunshot wound to face. Details of cheek laceration and left globe (eye) rupture and corneal scleral laceration included. The subject was scheduled for an outpatient corneal transplant. The subject discontinued the study due to AE of left eye globe rupture.																		
YKP3089C029- (b) (6)	23	F		86	(b) (6)	Abortion spontaneous	developed + HCG during ETOH interaction study. 1st Treatment on (b) (6) spontaneous abortion on (b) (6)																		
YKP3089C030- (b) (6)	71	M	200	2	(b) (6)	Hypertension	elevation of blood pressure to 180/84 on day 3 of study. Prior history of elevated BP																		

Reviewer Comment, SAE:

Examination of the SAEs in the phase 1 safety data reveal serious hypersensitivity events that may reflect the rapid cenobamate dose escalation at the time in the product development. These events also demonstrate the powerful pro-hypersensitivity potential of cenobamate, underscored by case YKP3089C018- (b) (6) (discontinuation) where signs and symptoms of a hypersensitivity syndrome began 7.8 hours after the 1st dose of cenobamate and case YKP3089C016- (b) (6) (SAE) where the hypersensitivity reaction began less than 4 hours after the 1st dose of cenobamate. In both of these cases the initial dose of cenobamate was 200mg and both had a 7 to 10-day course from onset to recovery. Intense CNS adverse effect is seen in a patient with characteristics of intoxication of sufficient severity to cause a fall. The report of spontaneous abortion where the fetus was likely exposed in the 1st 2 to 4 weeks of development have an uncertain relationship to cenobamate.

Treatment Emergent Adverse Events

The denominator for calculation of percent of the overall exposed phase 1 set is derived from the ISS, Phase 1 ADSL.xpt dataset including all but study AA41857 where the ADAE.xpt dataset contains no entries from this study. The denominator is therefore 1018 subjects.

The most frequent TEAEs >3% were “somnolence” (19%), “headache” (12%), “dizziness” (9%), “constipation” (8%), “nausea” (7%), “euphoric mood” (5%), “fatigue” (3%), “feeling of relaxation” (3%), “Vision blurred” (2%), “vomiting” (2%), “dermatitis contact” (2%), “dizziness postural” (2%), “diarrhoea” (2%), “GGT increased” (2%), “feeling hot” (2%), “Orthostatic heart rate response increased” (2%), “abdominal pain” (2%), and “weight decreased” (2%), see [Table 84](#) .

Table 84 Phase 1, Preferred Term Frequency >1%

Preferred Term	Subject Count	% Subjects
Somnolence	196	19
Headache	118	12
Dizziness	96	9
Constipation	82	8
Nausea	67	7
Euphoric mood	46	5
Fatigue	29	3
Feeling of relaxation	29	3
Vision blurred	25	2
Vomiting	24	2

Preferred Term	Subject Count	% Subjects
Dermatitis contact	22	2
Dizziness postural	21	2
Diarrhoea	20	2
Gamma-glutamyltransferase increased	18	2
Feeling hot	17	2
Orthostatic heart rate response increased	17	2
Abdominal pain	16	2
Weight decreased	16	2
Orthostatic heart rate response increased / Postural orthostatic tachycardia syndrome	31	3.0

Additional exploration if performed in SOC's of interest. In the "Gastrointestinal Disorders" SOC "nausea" and "vomiting" were most frequent. There was one withdrawal each for "nausea" and "vomiting", and an additional unique subject had an SAE entry for "nausea".

The SOCs "Immune system disorders" (1 entry) and "Skin and subcutaneous tissue disorders" were pooled for examination due to the potential to capture hypersensitivity events. There were 180 entries in these SOCs where the most frequent preferred terms with a frequency of $\geq 0.8\%$ were "dermatitis contact" (2.2% of Phase1 population), "Pruritus" (1.5% of Phase1 population), "rash papular" (0.9% of Phase1 population), "Pruritus generalized" ((0.8% of Phase1 population) and "rash macular" (0.8% of Phase1 population). From among these 5 terms, none is an SAE and there are 2 cenobamate withdrawals, both for the preferred term events of "rash macular".

An analysis of the pooled preferred terms "Postural orthostatic tachycardia syndrome", "Orthostatic heart rate response increased" and "dizziness postural" is performed. There were 58 adverse event entries under these preferred terms from 49 (4.8%) patients. Fifty-five (55) of these events were judged as "mild" severity by the investigator and 3 events of "dizziness postural" were judged as "moderate" severity. None was an SAE and none resulted in cenobamate withdrawal.

The preferred term "feeling hot" is explored for relationship to a hypersensitivity response. There were 20 "feeling hot" entries from 17 subjects. When this set of subject ID's is joined with the 180 entries from the SOCs "immune system disorders" and "Skin and subcutaneous tissue disorders" there is an overlap identified in 28 entries from 6 subjects where the overlapping preferred terms are shown in [Table 85](#) with the number of instances of each preferred term. None were entered as an SAE, there was one subject discontinuation associated with the preferred term "rash generalized" although these were entered as "mild" severity. Twenty six of 28 terms were entered as mild severity and 2 as "moderate" severity.

Table 85 Phase 1 AEs, SOC “immune system disorders” and “Respiratory, thoracic and mediastinal disorders” Instances of Overlap with the Preferred Term “feeling hot”.

Preferred term	instances
Rash papular	10
Dermatitis contact	4
Dermatitis	3
Erythema	3
Hyperhidrosis	2
Palmar erythema	2
Pruritus generalised	2
Rash generalised	2

Reviewer Comment:

Examination of the phase 1 study TEAEs, a cohort of subjects without prior exposure to and adaptation to antiepileptic drugs reveals that CNS adverse effects are the most prominent. Headache and gastrointestinal adverse effects are also frequent. There is a high frequency of “Orthostatic heart rate response increased” (2%). This is pooled with Postural orthostatic tachycardia syndrome”, and “dizziness postural” to yield a frequency of 4.8%. This points to a signal for change in peripheral vascular resistance, however, none of these events was an SAE or resulted in study drug withdrawal.

Adverse events associated with hypersensitivity with a frequency of 2% or greater are the preferred terms “dermatitis contact” and “feeling hot” where “feeling hot” was tested for concurrent association with events in the “Skin and subcutaneous tissue disorders”. These findings are in alignment with the pro-hypersensitivity characteristics of cenobamate.

Laboratory

Multiple dose Phase 1 studies unconfounded by concomitant AEDs are selected for examination. This method excludes DDI studies where phenobarbital, phenytoin, and carbamazepine are co-administered. This group of studies contains a pool of 246 subjects, see [Table 86](#).

Table 86 Core Phase 1 Studies for Laboratory Safety Data Analysis

STUDYID	Subjects
AA24143	50
YKP3089C009	20
YKP3089C018	30
YKP3089C020	108
YKP3089C026	38

Hematology

Hemoglobin

There were 173 instances from 48 subjects with normal baseline hemoglobin value that shifted to OORR low post baseline. The maximum negative shift was 2.1g/dl from a baseline of 13.4g/dl and the minimum overall value was 10.1 g/dl, a negative change from a baseline of 11.6 g/dl. The largest magnitude negative change from baseline was -15.7%. Mean and median percent change from baseline from among those with a post baseline OORR low value were -3.8% and -4.4% respectively. The distribution of change from baseline reveals that 9 of the 48 subjects had a positive percent change from baseline. There were 5 values from 3 subjects with a minimum value < 11g/dl.

Reviewer Comment, Hemoglobin:

Overall there is a signal for shift to post baseline OORR low hemoglobin values. There were 3 subjects with values between 11 and 10g/dl. No critical values were reached. The basis for the shift is uncertain. This may be related to study phlebotomy but a relation to cenobamate cannot be excluded.

Leukocytes

There were 31 instances from 15 subjects with normal baseline leukocyte value that declines to OORR low. The minimum value from among these events is 2.8×10^9 cells/L while the maximum percent change from baseline is -51%. The mean leukocyte count from this OORR low instances is 3.4×10^9 cells/L and the mean percent change from baseline is -28%. The overall mean percent change of all instances of leukocyte post baseline, on treatment measurements is -8.1%. Three subjects, YKP3089C020- (b) (6), YKP3089C018- (b) (6), YKP3089C018- (b) (6) with lowest post baseline values of 2.8×10^9 cells/L, 2.9×10^9 cells/L and 3.0×10^9 cells/L respectively had all leukocyte values obtained during study examined.

There were 10 instances from 6 subjects with normal baseline leukocyte value that had a post baseline increase to an OORR high value. The maximum percent change from baseline was 44% to a value of 13.8×10^9 cells/L.

The subject from study C020 (TQT)- YKP3089C020- (b) (6) remained in reference range after 30 days of treatment, then the low value emerged at approximately 60 days of treatment. This value improved in dechallenge interval of 5 days to 3.2×10^9 cells/L. The next subject, YKP3089C018- (b) (6) had a decline to 2.9×10^9 cells/L at 1st post baseline measurement at day 31. This rebounded to normal range after a 6-day dechallenge. The third subject, YKP3089C018- (b) (6), also from study C018 had a similar pattern with post baseline decline on day 31 to 3.0×10^9 cells/L then a rebound to 6.0×10^9 cells/L after a 6-day dechallenge.

Reviewer Comment, leukocytes:

There is a small signal for a decline in leukocytes associated with cenobamate treatment. In the majority of cases the decline is not below a threshold of 3.0×10^9 cells/L.

Neutrophils

There were 18 instances from subjects with normal baseline neutrophil count that declined to OORR low at any post baseline measurement while on cenobamate treatment. The minimum value recorded in 0.9×10^9 cells/L, all other OORR low values ranged between 1.1×10^9 cells/L and 1.8×10^9 cells/L. The mean value of all 18 OORR low instances was 1.44×10^9 cells/L. the maximum % change from baseline was -31% in the subject who had the nadir of 0.9×10^9 cells/L. the mean percent change of all instances of decline to OORR low was -34.5%. The lowest neutrophil value occurred in subject YKP3089C018- (b) (6) in study C018 occurred on treatment day 31 (only treatment measurement). The subsequent value 6 days later rebounded to 1.5×10^9 cells/L.

There were 6 instances from 6 subjects with a reference range neutrophil count that increased post baseline to an OORR high value. The maximum value was 11.6×10^9 cells/L which represented a 123% increase over baseline.

The mean percent change of all 737 neutrophil post baseline, on treatment measurements was -11.5% with a maximum percent decline from baseline of 61%.

Two subjects with a negative mean change from baseline are selected to examine the course of neutrophil counts during the study timeline. These subject are YKP3089C026- (b) (6) and YKP3089C020- (b) (6) with a mean change from baseline for all study measurements of -43% and -44.6% respectively. They also had 17 and 4 neutrophil measurements respectively. The results of the neutrophil value by study day and cenobamate dose for each of these two subjects is shown in [Figure 71](#) and [Figure 72](#).

Three subjects with the lowest neutrophil counts and change from baseline ranging from a minimum of 39% to a maximum of -61% are matched to the ADAE dataset to search for adverse events related to infection. One of the three, subject YKP3089C018- (b) (6) have 5 preferred term entries. None of these is from the “infections and infestations” SOC.

Figure 71 Subject YKP3089C026- (b) (6) Neutrophil Count and Change in Count from Baseline by Study Day and Cenobamate Dose

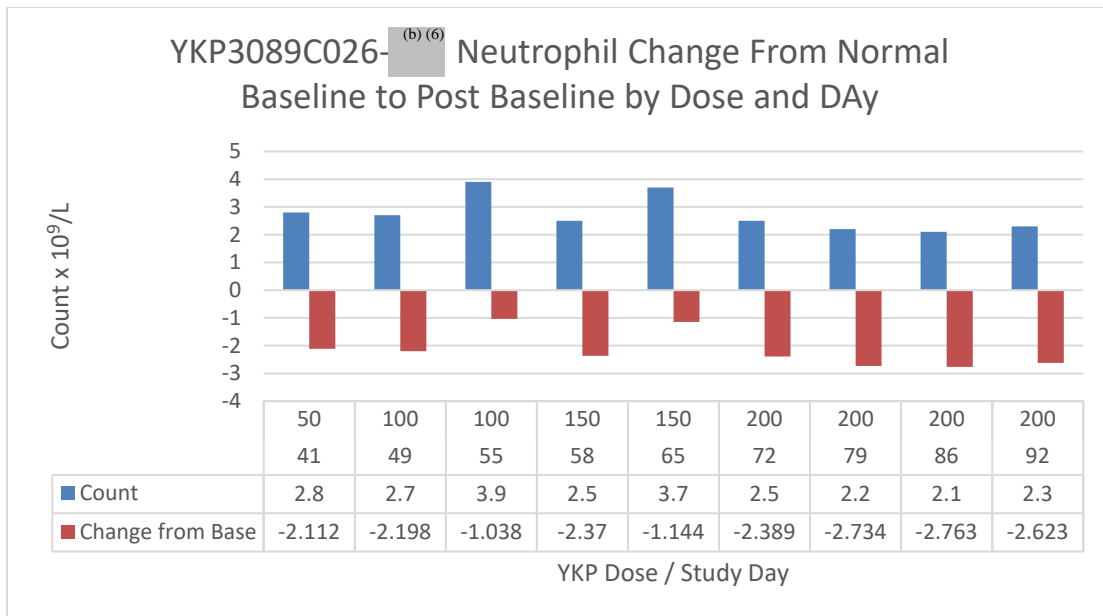
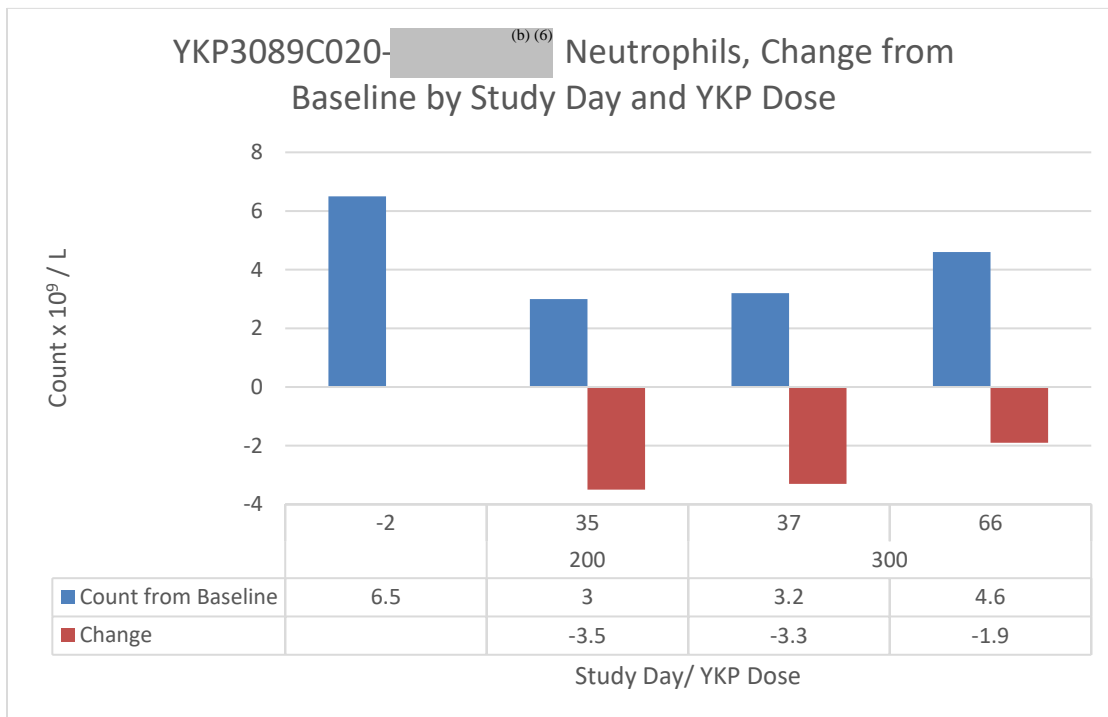


Figure 72 Subject YKP3089C020- (b) (6) Neutrophil Count and Change in Count from Baseline by Study Day and Cenobamate Dose



Reviewer comment, Neutrophils:

The post-baseline decline to OORR low values was in excess of the shift to OORR high values. The mean percent change of all 737 post baseline measurements from all subjects across the 5 studies was a decline of 11.5% from baseline value. Examination of neutrophil counts by patient across study measurements does not reveal a sustained decline in values. There is also no decline to critical neutropenia. There is a signal for decline in neutrophil values. The decline does not appear to be progressive, and it is rapidly reversible. A sample examination of the relationship between adverse events and the subjects with the lowest neutrophil counts does not reveal an occurrence of infections than would point to an effect on immunocompetence.

Platelets

Examination of the post baseline platelet counts reveals were 20 instances from 10 subjects. From among these there were 9 instances from three patients with baseline platelet values < 150×10^9 /L. In each of these cases there was a further decline from the OORR low baseline. The additional declines ranged from -13% to -18%. Among all OORR low values all but one were a decline from baseline. The mean change from baseline of all OORR low entries (post baseline) was -15%.

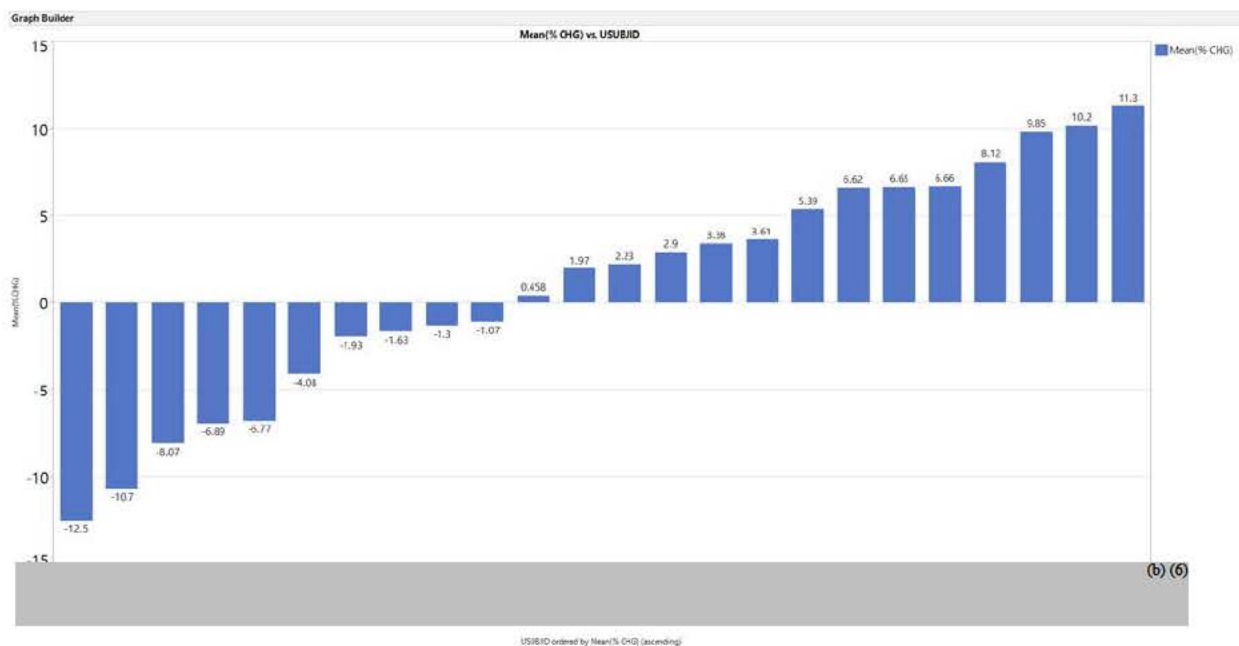
Subjects with OORR low post baseline values have all measurements examined. The number of samples is limited in most studies to draw conclusions on a sustained trend. Studies AA24143 and YKP3089C009 provide a baseline and single on treatment post baseline value (the OORR low post-baseline). Study YKP3089C020 provides a baseline, 2 on treatment and a day 1 post treatment value. This is useful for trend examination. In this study there are five subjects with an OORR low platelet count. Three of the five subjects have a trendline with a negative slope while two have a positive slope. In one subject all but one value including the baseline value is below 162,000. All subjects oscillate between increasing and decreasing post baseline values while in no case is there a sequential decline in platelet count at each successive measurement.

Examination of subjects in study YKP3089C026 have 16 post baseline platelet measurements over a period of 92 days. Two patients (YKP3089C026-^{(b) (6)} YKP3089C026-^{(b) (6)}) in this study had OORR low post baseline values. All platelet values are examined over the study timeline of these patients. This analysis reveals a trend for decreasing platelet value that is aligned with duration of exposure and increasing dose over the 92-day exposure span. Decline is not consistent with some oscillation around the trendline but an overall pattern of decline is present. In neither case does the platelet nadir drop to a critical value.

The overall trend of platelet counts in study C026 is examined due to the timeline and number of platelet measurements. Cenobamate dosing spans 12.5mg to 200mg during the 92-day study timeline. This extended timeline, dosing and measurement frequency will inform the behavior of platelet values. The mean percent change from baseline for each of the 24 subjects is calculated. There is a higher frequency of positive means than negative means. The distribution

is shown in Figure 73. The mean of all subject mean percent change from baseline is +1.0%. The minimum post baseline platelet count is $121 \times 10^9 /L$ and 6 entries have values $<140 \times 10^9 /L$. Those entries are from the two patients discussed in the above paragraph.

Figure 73 Phase 1, Platelets, Study C026, Mean % Change from Baseline by Subject



Reviewer Comment, platelets:

There are outlier subjects that have a trend of declining platelet count to OORR low values. Platelet values do not decline to a range of clinical concern or critical values. Overall, among the studies examined the frequency of decline in platelet value from baseline is greater than frequency of increase over baseline by a small margin. The analyses performed do not reveal a signal of concern for decline in platelet count.

Reviewer Comment, Hematology:

Hemoglobin, leukocytes, neutrophils and platelet values from 5 phase 1 studies in healthy subjects are examined. These studies were multiple dose studies with intervals not associated with concomitant medications. There was a trend toward a small decline with duration of treatment and increasing dose for all four parameters. The decline was not severe, critical thresholds were not reached, decline was inconsistent rather than sustained, and where dechallenge was observed at the end of study treatment values rapidly increased. The analyses do not reveal a safety signal for these hematology parameters.

Chemistry

ALT: there were 39 entries from 5 patients with ALT values >100 IU/L. Twenty (20) of these entries were from subject YKP3089C020- (b) (6) and 14 are from subject YKP3089C018-

(b) (6) Both of these subjects experienced DRESS syndrome and thus occur in the context of a severe hypersensitivity reaction. When subject (b) (6) and (b) (6) are excluded there are 5 remaining instances of ALT that are OORR high. Patient YKP3089C026-(b) (6) had a normal baseline with elevation to OORR high on study day 27. Values thereafter remained frequently OORR high over a period of 139 study days, with a peak on study day 68. Day sixty-eight (68) was 5 days after escalation to 150mg of cenobamate when value reached 3.5 x ULN then improved. In the remaining two patients from study C009 there were only sporadic elevations of ALT.

Two events from study C016 are considered from subject YKP3089C016-(b) (6) who also experienced a hypersensitivity syndrome.

Reviewer Comment, ALT:

DRESS syndrome that occurred in two patients accounted for 87% of all instances of OORR high ALT that were observed in the 5 phase 1 studies that were reviewed. From among the remaining instances, one subject had recurrent, sporadic elevations to OORR high. All other occurrences to OORR high were sporadic. The review does not reveal a notable signal for elevation of ALT among the healthy phase 1 subjects.

Alkaline Phosphatase: there were 16 entries from 4 patients with ALP values >132. A value of 132 IU/L is chosen because this is the highest upper boundary from among all entries for OORR high. From among these 4 patients the highest values (max. 218 IU/L) are seen in subject YKP3089C020-(b) (6) who had the severe DRESS reaction with a fatal outcome. From among the remaining 3 patients the maximum value is 186 IU/L, 1.4 x ULN. There is no signal for alkaline phosphatase elevation.

AST: there were 10 entries from 4 patients with an AST value. 2 x ULN. 7 of these 9 entries were from patient YKP3089C020-(b) (6) who had the severe DRESS reaction with a fatal outcome. From among the remaining three patients, one also had a diagnosis of DRESS on study day 14, with a maximum AST value of 173 (3.7 x ULN) on treatment day 24. This patient had cenobamate discontinued on treatment day 22. Subsequent AST values on treatment days 34 and 37 were within reference range. The next patient considered, YKP3089C020-(b) (6) had an elevation of AST to 3.2 x ULN on treatment day 78. This was 13 days after the last dose of cenobamate 500mg. An unscheduled measurement on study day 89 (post treatment day 23) revealed a value of 23 IU/L (.5 x ULN). The final patient, YKP3089C026-(b) (6) from among the four patients with AST elevations > 2 x ULN had excursions to 1.4 x ULN and 2.1 x ULN on cenobamate treatment days 20 and 23 respectively where dose was increased from 12.5mg to 25mg on treatment day 20.

Reviewer Comment, AST:

Examination of AST values reveals an increase associated with DRESS. The remaining OORR high events were sporadic, not sustained, and intermittent. A single delayed elevation at 23 days post treatment is sporadic. Overall there is no signal for elevation of AST values.

Bilirubin: There were 4 entries from 2 subjects with a normal baseline bilirubin value that shifted to OORR high at a post baseline measurement. None of these values exceeded 2 x ULN. One of these patients was YKP3089C020- (b) (6) who had DRESS syndrome with a fatal outcome. The maximum value in this case was 2.3 mg/dl (1.44 x ULN). In the remaining case, subject YKP3089C020- (b) (6) had a maximum total bilirubin value of 2.7 mg/dl (1.7 x ULN). This elevated value occurred on cenobamate treatment day 66, the day after last dose of 500mg cenobamate with no elevation of ALT, AST or Alkaline phosphatase. The subject also had elevation of direct bilirubin. The only adverse event entry in the ADAE dataset is constipation on study day 64. Two subsequent measurements were obtained on post treatment day 12 and 13 with bilirubin values of 1.8 (1.12 x ULN) and 1.7mg/dl (1.06 x ULN) respectively.

Reviewer Comment, Bilirubin:

Elevations to OORR high were associated with a severe hypersensitivity syndrome or were sporadic. Patient YKP3089C020- (b) (6) had elevation in both direct and total bilirubin with no concurrently associated laboratory abnormalities. The reason for this outlier is uncertain but does not appear to be a case of hepatocellular injury. Overall there is no signal for increase of bilirubin.

Bicarbonate: one non-baseline or screening bicarbonate value was OORR high. This was very close to reference range at 1.03 x ULN. There two patients with a normal baseline that had a decline to OORR low bicarbonate. One of these patients had a value that was 0.1mmol/L below RR at study day 17 and the second had a decline from baseline of 5.2mmol/L at study day 24 with a subsequent value within reference range at study day 37.

Reviewer Comment, bicarbonate:

There is no evidence of pathologic variation of bicarbonate.

Blood urea nitrogen (BUN): There were 7 entries from 7 subjects with BUN value OORR high. the maximum value was 28mg/dl, (RR 20mg/dl). To evaluate if these events were associated with a meaningful decline in renal function the range of BUN and Creatinine values across the study timelines were examined. this analysis cross laboratory test analysis reveals that in all 7 cases an increase followed by a decrease in creatinine and blood urea nitrogen values aligned with the onset and offset of cenobamate treatment. In one of seven cases the baseline creatinine was OORR high while in one case the baseline BUN was OORR high, see [Table 87](#). There were no entries for these subjects in the adverse event dataset.

Table 87 Phase 1, Subjects with OORR – High BUN, Corresponding Creatinine Values by Study Day and Cenobamate Dose

	Study day	BUN (RR 6-20)	Creat (RR 0.8-1.3)	Cenobamate dose
YKP3089C018- (b) (6)	-1	23	0.9	0
	22			500
	24	28	1.7	0
	34		1	0
	37	14	0.9	0
YKP3089C018- (b) (6)	-1	12	1	0
	21		1.4	600
	22		1.5	600
	23	21	1.4	600
	31		1.2	0
	34	17	1.2	0
YKP3089C009- (b) (6)	-1	16	1.07	0
	17			300
	18	12	1.1	0
	20	23	1.32	0
AA24143- (b) (6)	-1	13	1.05	0
	14			100
	15	18	1.35	0
	17	27	1.16	0
	19	19	1.11	0
AA24143- (b) (6)	-1	19	1.01	0
	14			100
	15	18	1.34	0
	17	25	1.15	0
	19	18	1.23	0
AA24143- (b) (6)	-1	21	1.13	0
	14			50
	15	17	1.32	0
	17	24	1.27	0
AA24143- (b) (6)	-1	19	1.12	0
	14			100
	15	16	1.25	0
	17	24	1.14	0
	19	19	1.17	0

Creatinine: In study AA24143 there are 6 (17%) subjects in the cenobamate treatment cohort with normal baseline creatinine that have an increase in creatinine value at study day 15, the day following final cenobamate dose. Creatinine values consistently decline toward baseline at post dose measurements. There was 1 (7%) subject in the placebo cohort with this same pattern of increase in dose associated creatinine value. One subject in the active cohort of

study YKP3089C009 with an elevation in creatinine at end of cenobamate (300mg) dosing and none in the placebo cohort. In study YKP3089C018 there were two subjects (10%) with an increase in creatinine to OORR high during cenobamate dosing that trended toward normal after completion of the dosing interval. There were none with this pattern in the inactive treatment group. In study C020 (TQT study) there were 8 subjects with an increase from normal baseline to an OORR high creatinine value during cenobamate treatment. This elevation was not sustained and in 5 cases improved while on continued cenobamate treatment. In two cases the maximum value occurred after cessation of cenobamate, subjects YKP3089C020- (b) (6) (11% over baseline) and YKP3089C020- (b) (6) (13% over baseline) . In study YUKP3089C026 there were 2 subjects with an elevation in creatinine over normal baseline. In both these cases the elevation normalized while cenobamate treatment was continued.

Reviewer Comment, Renal:

Examination of BUN revealed 7 cases with an elevation during cenobamate dosing. Evaluation of creatinine values in these 7 cases revealed the same trend. Subsequent examination of creatinine values revealed 20 subjects with a normal baseline creatinine and a post baseline excursion to OORR high. This trend was most consistent in study AA24143 while in study YKP3089C020 there were elevations of creatinine that improved as cenobamate treatment continued. In two cases a maximum value was recorded post treatment. The shift from the upper limit of normal generally did not exceed 15%. The implication of this observation is uncertain. The magnitude of increase in these phase 1 studies coupled with the observation of very uncommon sustained sequence of elevated values does not appear to be a signal in the pivotal studies for renal dysfunction associated with cenobamate treatment.

The sponsor also identifies this signal in the phase 1 population with the following entry in the ISS section 5.2.4 Clinical Chemistry, Phase 1 Pool:

The most frequent abnormal post-baseline clinical chemistry parameters observed in ≥50 subjects include the following:

- Glucose: 70/401 (17.5%) subjects
- Creatinine: 61/401 (15.2%) subjects

There were no clinically important signs and symptoms associated with these abnormal post-baseline clinical chemistry parameters.

C-Reactive Protein: C reactive protein is captured in study YKP3089C026. There were 4 post baseline OORR high values. Examination of all values in the study reveals these abnormal values are sporadic and not part of a sustained or escalating trend associated with cenobamate dosing.

Calcium: Calcium values are examined. there were 4 entries for 4 patients with a single elevation of calcium OORR high. These were sporadic values not part of a sustained or

escalating trend associated with cenobamate dosing. There were 7 entries from 4 patients. These were also sporadic values on the study timeline.

Chloride: There were 5 post baseline OORR low chloride values from 4 subjects. The trend for these subjects was examined and these values were found to be isolated or sporadic or both. There were no OORR High chloride values.

Creatinine Phosphokinase (CPK, CK)

There were 35 entries from 20 subjects in 7 phase 1 studies with on active cenobamate treatment with a post baseline CK value > 400 IU/L. The maximum CK value was 4434 in study C026.

The adverse event dataset of these subjects is examined for related terms. There were 55 adverse event from 34 preferred terms. None was entered as an SAE, all were judged “mild” or “moderate” severity. There was one drug withdrawal due to and event of “Subcutaneous abscess”. There were 7 subjects with an entry for “Blood creatine phosphokinase increased”. There was one entry each for the muscle related terms “muscle spasms”, “musculoskeletal discomfort” and “muscle twitching”.

Examination of the complete profile of CK entries for the 20 subjects with identified CK > 400 IU/L reveals that recordings of elevate CK are sporadic, occur on a background of high pre-treatment values, or occur at the lowest cenobamate dose then return to normal as dose increases. There were 3 patients with a post dose elevation followed by decline after cessation, see [Table 88](#).

Reviewer Comment, Serum CPK:

Detailed examination of the CK elevations in the phase 1 studies reveals 3 instances that are related to cenobamate treatment, have a directional trend to related to treatment or dechallenge response to cessation of treatment. The majority are sporadic events or do not have clear coupling to cenobamate treatment. In one case there is an inverse relationship to dosing where the CK level declines as cenobamate dose increases. Although on initial exam the frequency of elevated serum CK values caused concern, close examination of the CK values of each measurement for all patients does not reveal a signal for cenobamate related CK elevation.

Table 88 Phase 1 CK Analysis

USUBJID	Max	Episodic- Sporadic	other	non sustained	events
AA22780- (b) (6)	422	Y		Y	1
AA22780- (b) (6)	430			Y	2
AA24143- (b) (6)	126 9	trend	peak post day 3 then decline post 5, 12 (still OORR H)	N	3
AA24143- (b) (6)	504		Peak post day 2	Y	1
AA24143- (b) (6)	419		Peak post day 2	Y	1
AA24143- (b) (6)	211 4	trend	peak post day 2, then decline to RR	N	3
AA24143- (b) (6)	847	Y	peak mid treatment	Y	2
AA24143- (b) (6)			pre treat only		
AA41857- (b) (6)	621		pre treat max		
YKP3089C009- (b) (6)	672	trend	post treat peak then decline		2
YKP3089C016- (b) (6)		OORR high screening and sporadic	Peak 14 days post dose, O		3
YKP3089C016- (b) (6)	184 1	OORR High pre YKP, sporadic high			6
YKP3089C026- (b) (6)	624	sporadic			1
YKP3089C026- (b) (6)	769	sporadic			4
YKP3089C026- (b) (6)	542	single episode post treatment	day 125		1
YKP3089C026- (b) (6)	615	single episode post treatment	day 125		
YKP3089C026- (b) (6)	443 4		peak at 12.5mg, declines to RR as dose progresses to 100mg, 130 IU/L at dose of 200mg		3
YKP3089C029- (b) (6)		single episode at 200mg single dose not repeated on second			
YKP3089C029- (b) (6)		event 42 days after final 200mg dose	unrelated		1
YKP3089C029- (b) (6)		event 21 days after dose of 200mg	unrelated		2

Glucose:

Examination of glucose values in the Phase 1 safety dataset (Table 86) are examined. In subjects with normal baseline glucose values there were 17 entries from 14 patients with a post baseline glucose value OORR high or low, based on a composite reference range of 70mg/dl to 110mg/dl for the select studies. Four (1.6%) patients had an OORR low value while 10 (4.0%) patients had an OORR high value. The maximum shift to high was a value of 122 from a baseline of 106 while the maximum low shift was to a value of 63 from a baseline of 97. A scatterplot with trendline of each of these 14 patients is examined. Eight patients have a positive slope where in 3 cases there is a clear systematic trend. Six patients have a negative slope across study glucose values. Both the high and low shift from baseline of greatest magnitude were 35%.

Reviewer Comment, Glucose:

There is a small excess of elevation of glucose over shift to low glucose. There is a small signal for glucose elevation that does not reach a level of clinical concern.

Potassium: Examination of potassium values reveals an excess of shift from normal baseline to OORR low. There were 27 instances from 14 (5.7%) subjects with an OORR low post baseline potassium value and 1 (0.4%) subject with a normal baseline and subsequent post baseline OORR high value. There was 1 patient with a shift to 3.1meq/L from 3.9 meq/L. The remaining 13 subjects had shifts to 3.4 meq/L or higher. Three subjects with potassium of < 3.5 meq/L are examined for the potassium value trend across the study timeline. In two subjects the low potassium value was sporadic while in the remaining subject (YKP3089C018- (b) (6)) there was a consistent trend across measurements. This latter subject was withdrawn from on study day 1 due to a hypersensitivity reaction.

Reviewer Comment: potassium:

Overall, there was an excess of low post-baseline outliers. There is a signal for a cenobamate influence to reduce potassium values, but the effect is not manifest as a strong consistent trend and does not lead to critically low values.

Sodium: Examination of post-baseline, on treatment sodium values from the selected phase 1 studies reveals no OORR high values. There were 6 OORR low values from 5 subjects. 4 of these subjects had a value of 134 meq/L while one subject (YKP3089C018- (b) (6)) had a value of 122meq/L. This latter subject also had an SAE due to DRESS and was discontinued from the study. The shift to low of 134 from the low boundary of reference range 135meq/L is small.

Reviewer Comment, sodium:

Overall there is no signal for hyponatremia due to cenobamate treatment in healthy subjects.

Reviewer Comment, chemistry:

Areas of concern that were identified include elevation of ALT but only in the context of and independently driven hypersensitivity reaction rather than a primary DILI. Assessment of AST

did not identify a signal that reached a level of clinical concern. Sustained or sequentially escalating bilirubin levels were associated with a severe hypersensitive reaction. There was a shift to increase of creatinine in approximately 3% of patient. These measurements were generally sporadic and in one case after an elevation continued to decline as cenobamate dose increased. This observation does not reach the level of a signal of clinical concern. Frequent elevations of serum CPK were identified. Among these elevations the highest were sporadic without sequential elevation. No trend of sustained sequential CPK elevation was identified. Examination of glucose levels reveals a small trend to elevation with an excess of post baseline shift to OORR high values over shift to OORR low. The maximum values were not highly elevated OORR. There was no sustained sequential trend among subjects. Assessment of potassium revealed an excess of post baseline shift to OORR high over OORR low values. The effect was not manifest as a strong consistent trend and does not lead to critical low values.

Vital Signs

The sponsor analysis of vital signs in the Phase 1 pool reveals an increase in systolic blood pressure in the aggregate of post baseline measurements. There is also a notable decrease in pulse where 66% of patients had a heart rate measurement <60 beats per minute.

Table 89 Phase 1 Pool, Post Baseline Vital Signs (from ISS, Table 6, p140)

Category	Total n (%)
Systolic blood pressure (mmHg) (N=535)	
<90	59 (11.0)
>140	163 (30.5)
>160	18 (3.4)
Diastolic blood pressure (mmHg) (N=535)	
<50	76 (14.2)
>90 to ≤100	109 (20.4)
>100	34 (6.4)
Pulse rate (bpm) (N=535)	
<60	352 (65.8)
>100	138 (25.8)
Weight (N=70)	
Decrease of ≥7% from baseline	0 (0.0)
Increase of ≥7% from baseline	0 (0.0)
Temperature (°C) (N=434)	
<36.0	168 (38.7)
>38.0	3 (0.7)
Respiratory rate (breaths/minute) (N=343)	
<12	67 (19.5)
>20	20 (5.8)

To assess effect of cenobamate on heart rate study AA22780 is examined. This study is chosen because it allows analysis of the effect on heart rate over a period of one day after a single dose of cenobamate across a range of doses in a meaningful sample size. Heart rate is of interest due

to the observation of 66% with a value <60 bpm. In addition, the adverse event dataset contains entries for postural tachycardia in 3% of subjects, see [Table 84](#). Analysis of study single ascending dose study AA22780, 1-minute sitting pulse, reveals a trend of increasing heart rate in the post dose interval up to the to 7.83 hours as shown in [Figure 74](#). Based on trendlines this has qualitative dose response, however in each dose interval the frequency of shift to increase in heart rate is similar to the shift to a decreased heart rate.

The trend in standing 1-minute pulse reveals an increasing trend in heart rate in the post dose interval up to hour 5.83 without a notable dose or treatment response. The placebo arm has a trendline slope that is similar to the trendline slope of the 200mg, 300mg, 400mg dose and greater than the 750mg trendline, [Table 90](#). The change from baseline shifts from low to high and high to low are similar in each dose group with no trend on qualitative examination, [Figure 75](#).

Table 90 Study AA22780 Standing Pulse, 1 minute by Post Dose and Dose Group Trendline Slope

Dose (mg)	Trendline slope
Placebo (0)	3.3
10	3.0
25	2.9
50	4.5
100	2.4
200	3.6
300	3.3
400	3.4
500	3.4
600	4.7
750	2.4

The systolic standing blood pressure values across post dose hours 1.83 to 5.83 by dose group are examined by mean, median, minimum (of group), and maximum (by group). This analysis reveals a small mean negative change with a peak in the 500mg dose group and maximum at hour 3.83 with a value of -13mmhg (group mean). The median changes are also in alignment with the mean observations. Examination of the minimum and maximum for each group and time reveals some excess in the magnitude of maximum decline in systolic pressure over maximum increase in systolic blood pressure but at 3.83 hours and 5.83 hours the placebo arm has the largest negative change from baseline.

Reviewer Comment, Vital Signs:

There is a trend of increasing heart rate in the post-dose hours which is without a dose response and which is similar to the trend seen in placebo. There is a mean decline in standing systolic blood pressure with a maximum of -13mmHg at 3.83 hours in the 500mg dose group which then improves in the 600mg and 750mg dose groups. Overall, there is some trend for an

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increase in heart rate and decrease in systolic blood pressure following a single dose of cenobamate, a dose response is not sustained and for heart rate, there is no clear separation from placebo.

Figure 74 Phase 1, Study AA22780, Post-Baseline Sitting 1-minute Pulse, Measurements at Hours 1.83, 2.83, 3.83, 5.83, and 7.83. Dose Range 5mg to 750mg (PBO=0). All Patients with Baseline < 55 BPM Excluded. Change from baseline represented by blue (-50 bpm) to white (+40 bpm) gradient

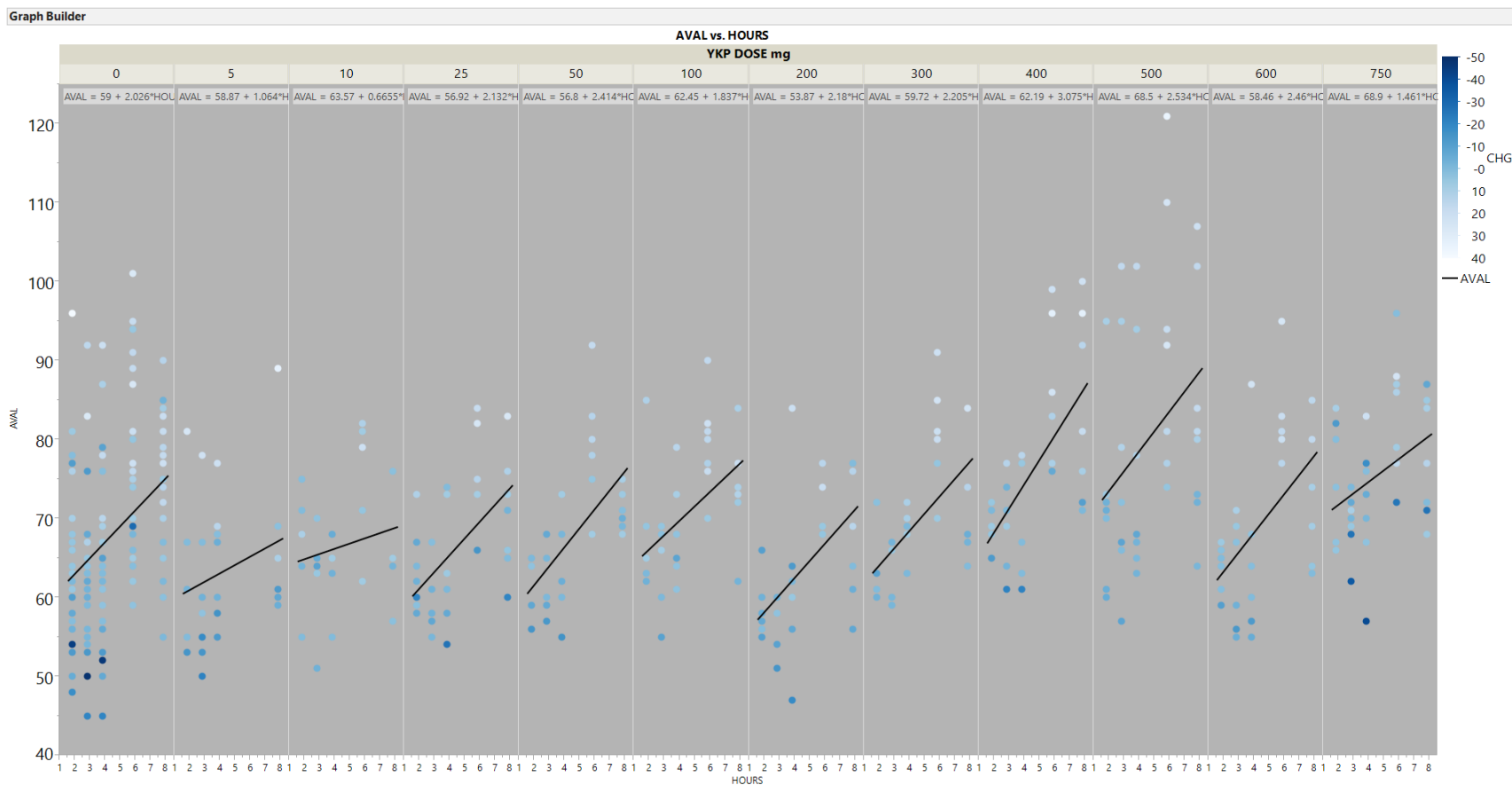
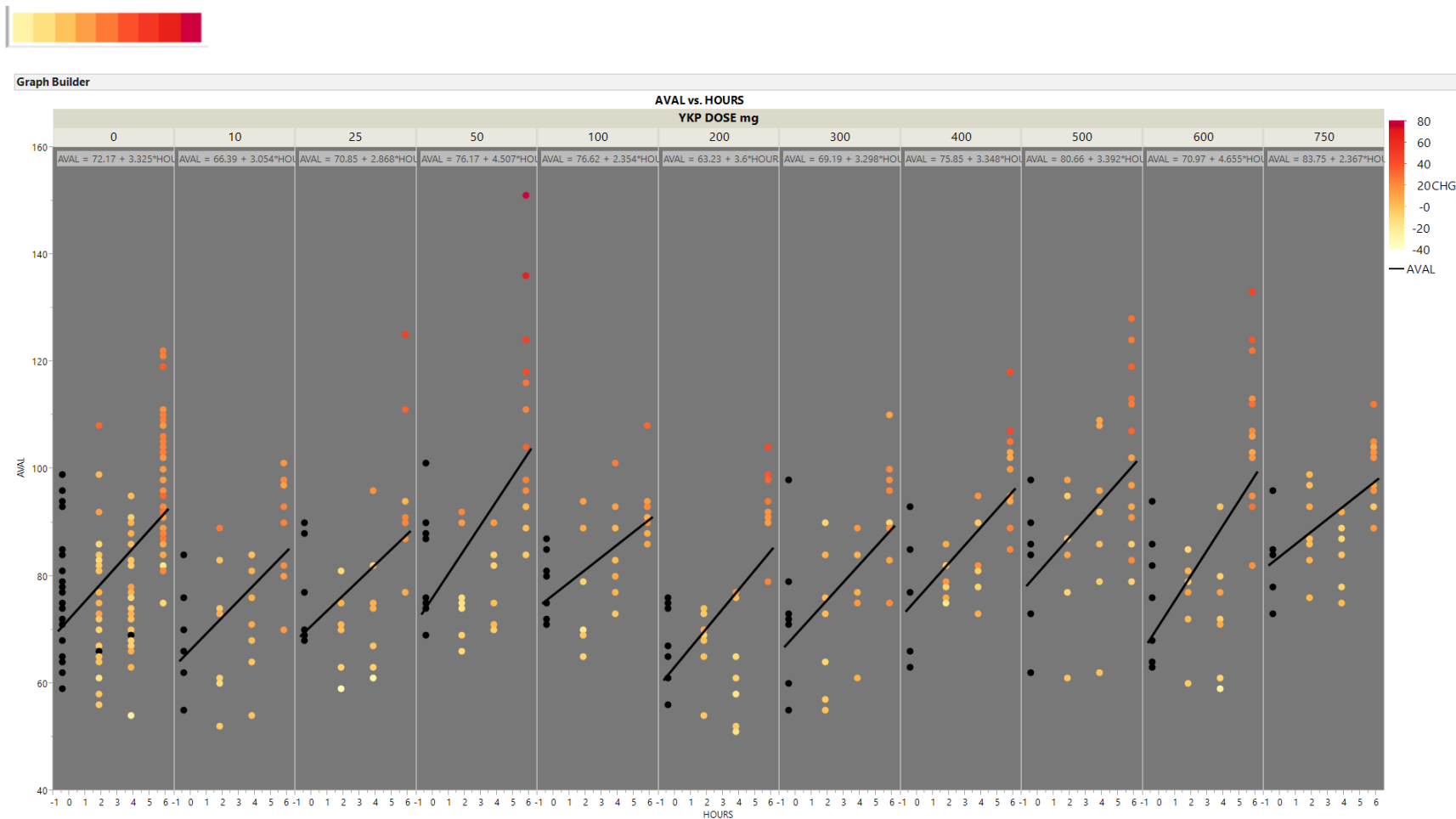


Figure 75 Phase 1, Study AA22780, Standing 1-minute Pulse, Measurements at Baseline, Hours: 1.83, 2.83, 3.83, and 5.83. Dose Range 5mg to 750mg (PBO=0). Change from baseline represented by yellow (-40 bpm) to orange (+80 bpm) gradient



ECG

The sponsor reports some instances of post baseline QTcB and QTcF prolongation. For QTcF these are shown as 1 (0.3%) subject with a value in the range >480 to ≤500 and 13 (3.8%) subjects with a post baseline value in the range >450 to ≤480.

To further evaluate the overall phase 1 ECG results the ADEG dataset is examined. The row entry of the parameter variable is summarized to search for abnormal entries as shown in xx. The timing and values of the 4 entries with an intraventricular conduction delay and entries of prolonged QT are examined.

The intraventricular conduction delays all occurred in study C020 from subjects YKP3089C020- (b) (6), YKP3089C020- (b) (6), and YKP3089C020- (b) (6) where there are ECG entries from days 1, 35, 42, 63, 65, and 78. All were on active treatment. All had baseline QRS duration > 100ms. There was no consistent dose response to QRS duration. In two subjects the maximum change from baseline value was 6 ms while in the third the maximum change was 8ms that occurred between baseline and 1st post dose measurement (100mg YKP), [Figure 76](#).

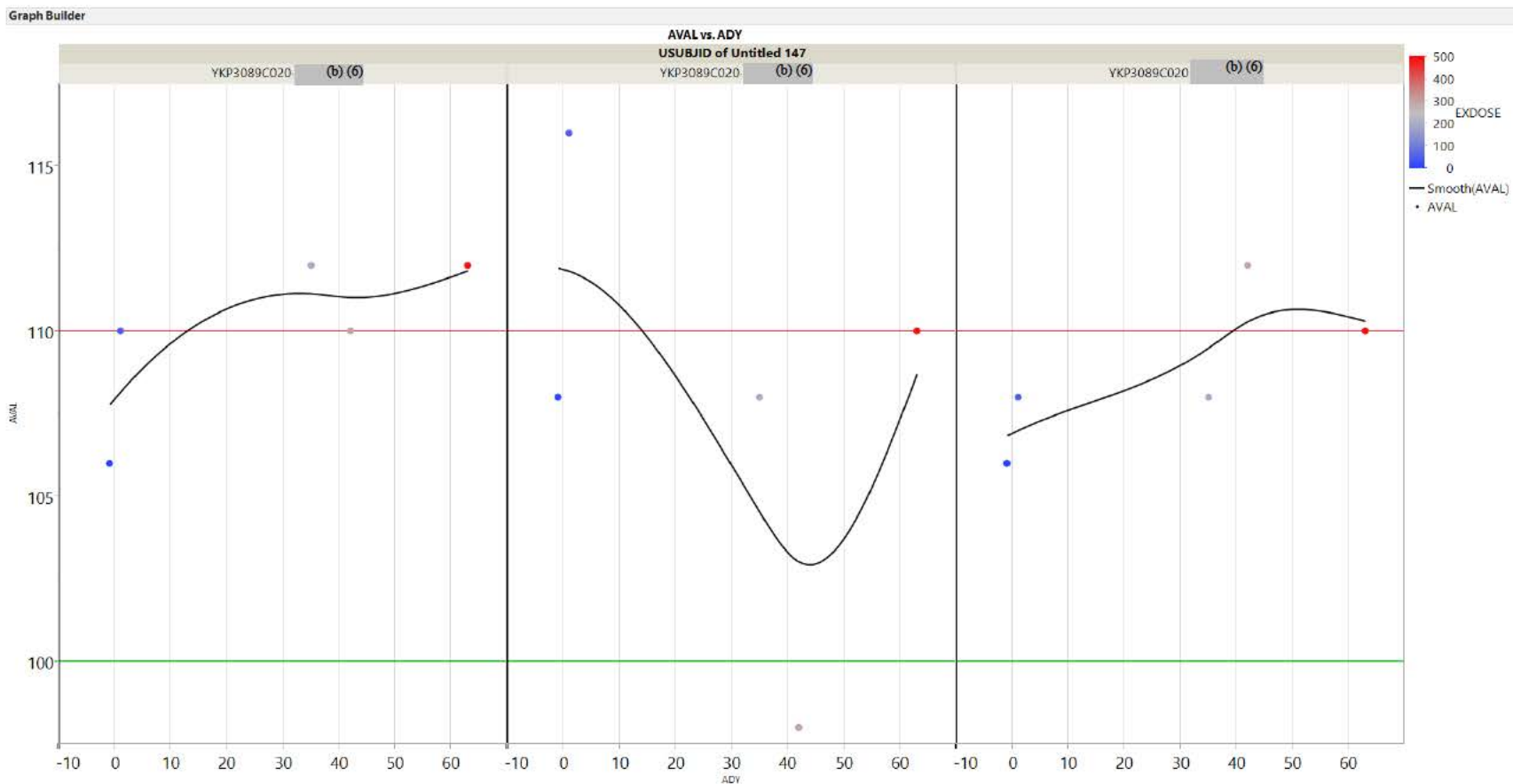
Table 91 Phase 1 Studies, ECG Interpretation Variable.

Entries for Variable "PARAM" Value "Interpretation" ISS Phase 1 ECG Dataset	Instances of Entry
NORMAL	4464
NORMAL; SINUS BRADYCARDIA	20
NORMAL; SINUS ARRHYTHMIA	12
ABNORMAL NCS	1907
ABNORMAL	461
ABNORMAL; BORDERLINE PROLONGED QTC	4
ABNORMAL; FIRST DEGREE ATRIOVENTRICULAR BLOCK	4
ABNORMAL; SHORT PR INTERVAL	4
ABNORMAL; INTRAVENTRICULAR CONDUCTION DELAY, NONSPECIFIC	2
ABNORMAL; INTRAVENTRICULAR CONDUCTION DELAY, NONSPECIFIC; SINUS BRADYCARDIA	2
ABNORMAL (CS)	1
ABNORMAL; BORDERLINE PROLONGED QTC, FIRST DEGREE ATRIOVENTRICULAR BLOCK. SAFETY NURSE LT12 AND PI DS11 NOTIFIED OF OUT OF RANGE QT VALUE	1
ABNORMAL; BORDERLINE PROLONGED QTC, FIRST DEGREE ATRIOVENTRICULAR BLOCK. RECHECK DUE TO OUT OF RANGE QT VALUE	1
ABNORMAL; BORDERLINE PROLONGED QTC. RECHECK DUE TO OUT OF RANGE QT VALUE	1
ABNORMAL; BORDERLINE PROLONGED QTC; SINUS ARRHYTHMIA. SINUS BRADYCARDIA	1
ABNORMAL; INCOMPLETE RIGHT BUNDLE BRANCH BLOCK	1
ABNORMAL; POOR R WAVE PROGRESSION; SINUS BRADYCARDIA	1
ABNORMAL; PREMATURE ATRIAL COMPLEX; SINUS BRADYCARDIA	1
ABNORMAL; PREMATURE VENTRICULAR COMPLEX	1

ABNORMAL; QTC PROLONGATION	1
ABNORMAL; QTC PROLONGATION. SINUS BRADYCARDIA	1
ABNORMAL; SINUS ARRHYTHMIA	1

The QT of subjects with an interpretation of prolonged QT are examined to identify the QTcF value. Any interpretation of prolonged QTc or that contains “borderline prolonged QTc “ is captured. There were 12 patients that were identified in this category. The QTcF values across study measurements for all entries of these 12 patients were examined. From among these patients there 6 with a post baseline QTcF value > 450msec where the maximum was 468 msec. This was associated with a 20 msec increase over baseline. Where a baseline value is included, the change from baseline from all 12 patient at all study visits is examined to determine the frequency of QTcF increase compared to QTcF decrease. This analysis reveals there were 30 instances of post baseline increase in QTcF with a mean and median of 18.1 msec and 15.5 msec respectively. There were 40 instances among the QTc measurements where there was a QTcF decrease from baseline with a mean and median of -14.9 and -12 msec respectively. There were 2 instances of no change from baseline. The maximum negative change from baseline was -42 msec while the maximum increase from baseline was +53 msec. Overall the analysis of QTcF across post baseline study visits among these 12 patients does not reveal a consistent trend of QTcF prolongation.

Figure 76 Phase 1, ECG, 3 Subjects with IV Conduction Delay by QRS Duration, Study Day, Subject and Dose (color gradient blue to red, 100mg to 500mg)



Reviewer Comment, ECG:

The overall ECG examination does not reveal a signal for consistent QTc or intraventricular conduction prolongation.

Adverse Events Associated with Cessation of Cenobamate Treatment

Cenobamate has mean elimination half-life ranged from 50 to 60 hours. This property may ameliorate withdraw signs and symptoms because the slow decay of cenobamate concentration allows time for adaptation to the loss of pharmacodynamic effects of the drug. However, withdrawal effects may occur. The phase 1 studies offer the opportunity to identify effects in a population of subjects that have not adapted to the chronic background central nervous system effects of Antiepilepsy drugs. Therefore, selected phase 1 studies were examined for features of drug withdrawal.

Table 92 Phase 1 Studies Chosen to Examine for Withdrawal Adverse Events, Study ID, Dosing, Design, and Purpose

STUDYID	dose	Design	purpose	peak dose	Study Duration	PBO n	YKP n	YKP Treatment Duration	post YKP Study day
AA24143	MAD		PK	200	17	15	35	14	14
YKP3089C006	multiple dose, 1/pd	1 sequence, 3 Period	PK-contraceptive	100	35		28	30	35
YKP3089C009	MAD		PK 250-300mg	300	17	6	14	17	18
YKP3089C018	MAD	3 sequence, 4 period	PK titration	600	29	9	21	29	30
YKP3089C020	multiple	3 sequence, 3 Period	TQT	500	65	54	52	64	66
YKP3089C026	multiple	1 sequence	Interaction with P450 probe3	200	109	0	24	98	110

An analysis of adverse event potentially associated with cenobamate withdrawal was performed. Multiple dose phase 1 studies were selected that were did not have intervals of concomitant treatment with additional AEDs. Six studies were selected, these included AA24143, YKP3089C006, YKP3089C009, YKP3089C018, YKP3089C020, and YKP3089C026. There were 274 healthy subjects in these studies where the end day ranged from 14 days to 110 days, see [Table 92](#). The phase 1 ISS, ADAE dataset was the source of adverse event preferred terms that were searched for potential withdrawal events. All adverse event entries that occurred on or after the treatment end date were captured from the six studies. This method captured 192 entries containing 105 preferred terms from 62 subjects that had an adverse event start date on or after the treatment end date where the treatment included cenobamate. The complete preferred term list is shown in [Table 93](#).

From among the adverse events that were captured by this method a set of preferred terms were selected that may be associated with central nervous system stimulation or mood disorder. This category of adverse event yielded a group of 25 preferred terms from among the 92 instances of post treatment adverse effects. Adverse events that occurred later than 20 days from end of treatment are excluded. This exclusion yielded a final count of 45 adverse event entries from 25 subjects. These preferred terms with the number of subjects that experienced each of the adverse events and the time of adverse event from end of treatment is shown in [Table 94](#).

The causality of adverse events that occurred on the last day of study drug treatment is less likely. The relationship of the time of last dose to time of event is important since the longer interval from last dose the greater likelihood the experience may be due to absence of the drug treatment. This fine structure of temporal relationship was not captured by the reviewer but day 0 events are captured.

The analysis revealed the most frequent events, with greater than 1 occurrence were the preferred terms “insomnia”, “headache”, “decreased appetite”, “depressed mood”, “discomfort”, “fatigue”, “feeling hot”, “head discomfort” and “tremor”. The term headache is very common in all safety datasets in the development program, therefore is very non-specific. The causal relationship of fatigue to drug withdrawal is weak but the non-specific nature of fatigue also allows for overlap with mood disorders and may be a surrogate for a depressed state. Single occurrence preferred terms that have a high likelihood of causal relationship to drug withdrawal are “body temperature increased”, “chills”, “heart rate increased”, “nervousness”, “nightmare”, and “tachycardia” because these events are seen with rebound of sympathetic nervous system, see [Table 94](#).

An examination of time to onset of a given event may add to the causal strength of association. Events that occur in the more rapid phase of decline of cenobamate concentration are more suspect as withdrawal phenomena. All but two events occur within 8 days of cenobamate discontinuation. This represents approximately 3.2 half-lives of the drug, so these events are plausibly related to the decay of cenobamate concentration. The final two events that are listed in [Table 94](#) occur 20 days after discontinuation and are less likely related to withdrawal.

Table 93 Phase 1, Withdrawal Adverse Event Evaluation, All Post Treatment Preferred Terms from 6 Selected Studies (healthy subjects)	
preferred term	
Abdominal distension	Libido decreased
Abdominal pain upper	Lip pain
Acne	Lip swelling
Alanine aminotransferase increased	Lymph node pain
Alopecia	Lymphadenopathy
Amnesia	Mental status changes
Anxiety	Myalgia
Aphasia	Nasal congestion
Asthenia	Nausea
Back pain	Neck pain
Balance disorder	Nervousness
Blood alkaline phosphatase increased	Nightmare
Blood creatine phosphokinase increased	Nystagmus
Body temperature increased	Ocular hyperaemia
Bradypnea	Odynophagia
Burning sensation	Oedema peripheral
Cerumen impaction	Oral papule
Cheilitis	Oropharyngeal pain
Chest discomfort	Orthostatic hypotension
Chest pain	Pain
Chills	Pain in extremity
Constipation	Palatal oedema
Cough	Palpitations
Decreased appetite	Paraesthesia
Depressed mood	Periorbital haemorrhage
Depression	Photophobia
Dermatitis contact	Postural orthostatic tachycardia syndrome
Diarrhoea	Presyncope
Discomfort	Pruritus generalised
Dizziness	Rash
Dizziness postural	Rash generalised
Drug hypersensitivity	Rash macular
Drug reaction with eosinophilia and systemic symptoms	Rash papular
Dry eye	Scleral hyperaemia
Dry skin	Skin abrasion
Dysmenorrhoea	Skin burning sensation
Dyspnoea	Sneezing
Ecchymosis	Somnolence
Eosinophilic myocarditis	Suicidal ideation
Erythema	Sunburn
Eye irritation	Swelling face
Eye pain	Tachycardia
Fatigue	Tinea cruris
Feeling hot	Tinnitus
Feeling jittery	Tonsillar hypertrophy
Gamma-glutamyltransferase increased	Tremor
Head discomfort	Urinary tract infection
Head injury	Vaginal discharge
Headache	Vertigo
Heart rate increased	Vision blurred
Insomnia	Vomiting

Table 93 Phase 1, Withdrawal Adverse Event Evaluation, All Post Treatment Preferred Terms from 6 Selected Studies (healthy subjects)	
preferred term	
Joint dislocation	Weight decreased
Laceration	

Table 94 Phase 1, Adverse Events Potentially Associated with Cenobamate Withdrawal by Frequency and Time from End of Treatment			
Frequency of Preferred Terms		Time to Event from End of Treatment (days)	
Preferred Term	# Subjects	Preferred Term	# Days
Insomnia	7	Anxiety	0
Headache	5	Chills	0
Decreased appetite	4	Depression	0
Depressed mood	2	Headache	0
Discomfort	2	Heart rate increased	0
Fatigue	2	Aphasia	1
Feeling hot	2	Decreased appetite	1
Head discomfort	2	Discomfort	1
Tremor	2	Fatigue	1
Anxiety	1	Feeling hot	1
Aphasia	1	Headache	1
Body temperature increased	1	Insomnia	1
Chest discomfort	1	Skin burning sensation	1
Chest pain	1	Discomfort	2
Chills	1	Feeling hot	2
Depression	1	Headache	2
Heart rate increased	1	Insomnia	2
Nervousness	1	Tachycardia	2
Nightmare	1	Chest discomfort	3
Photophobia	1	Decreased appetite	3
Skin burning sensation	1	Fatigue	3
Suicidal ideation	1	Insomnia	3
Tachycardia	1	Nightmare	3
		Photophobia	3
		Tremor	3
		Tremor	4
		Decreased appetite	5
		Depressed mood	5
		Head discomfort	5
		Suicidal ideation	5
		Nervousness	6
		Body temperature increased	7
		Depressed mood	7
		Insomnia	7
		Decreased appetite	8
		Headache	8
		Insomnia	8
		Chest pain	20
		Head discomfort	20

Reviewer Comment, Withdrawal

The temporal relationship and the implied medial physiology of several preferred terms identified during the end of treatment interval are consistent with a cenobamate withdrawal effect. The terms most likely to have a causal relationship are “insomnia”, “anxiety”, “depressed mood”, “nightmare”, “decreased appetite”, “tremor”, “body temperature increased”, “chills”, “heart rate increased”, “nervousness”, “nightmare”, and “tachycardia”.

8.5.1. Phase 1 Safety Summary

The most prominent SAEs related to cenobamate treatment were DRESS events. This identifies a pro-hypersensitivity property of cenobamate and emerged in the phase 1 studies where dose escalation was rapid. The remaining SAEs were unrelated to cenobamate. Examination of the phase 1 study TEAEs, a cohort of subjects without prior exposure to and adaptation to antiepileptic drugs reveals that CNS adverse effects are the most prominent. Headache and gastrointestinal adverse effects are also frequent. There is a high frequency of “Orthostatic heart rate response increased” (2%). This is pooled with Postural orthostatic tachycardia syndrome”, and “dizziness postural” to yield a frequency of 4.8%. This points to a signal for change in peripheral vascular resistance, however, none of these events was an SAE or resulted in study drug withdrawal. These events may be mechanistically related to the trend in vital signs where an increase in post dose heart rate and a small mean negative change in systolic blood pressure was observed in examination of study AA22780.

Adverse events associated with hypersensitivity with a frequency of 2% or greater are the preferred terms “dermatitis contact” and “feeling hot” where “feeling hot” was tested for concurrent association with events in the “Skin and subcutaneous tissue disorders”. These findings are in alignment with the pro-hypersensitivity characteristics of cenobamate. mate or uncommon outlier events of uncertain relationship.

Hemoglobin, leukocytes, neutrophils and platelet values from 5 phase 1 studies in healthy subjects are examined. These studies were multiple dose studies with intervals not associated with concomitant medications. There was a trend toward a small decline with duration of treatment and increasing dose for all four parameters. The decline was not severe, critical thresholds were not reached, decline was inconsistent rather than sustained, and where dechallenge was observed at the end of study treatment values rapidly increased. The analyses do not reveal a safety signal for these hematology parameters.

Areas of concern that were identified include elevation of ALT but only in the context of and independently driven hypersensitivity reaction rather than a primary DILI. Assessment of AST did not identify a signal that reached a level of clinical concern. Sustained or sequentially

escalating bilirubin levels were associated with a severe hypersensitive reaction. There was a shift to increase of creatinine in approximately 3% of patient. These measurements were generally sporadic and in one case after an elevation continued to decline as cenobamate dose increased. This observation does not reach the level of a signal of clinical concern. Frequent elevations of serum CPK were identified. Among these elevations the highest were sporadic without sequential elevation. No trend of sustained sequential CPK elevation was identified. Examination of glucose levels reveals a small trend to elevation with an excess of post baseline shift to OORR high values over shift to OORR low. The maximum values were not highly elevated OORR. There was no sustained sequential trend among subjects. Assessment of potassium revealed an excess of post baseline shift to OORR high over OORR low values. The effect was not manifest as a strong consistent trend and does not lead to critical low values. There was no shift trend or outlier effect seen on serum sodium.

Analysis of the phase 1 data for potential withdrawal adverse effects does reveal a positive signal. The temporal relationship and the implied medial physiology of several preferred terms identified during the end of treatment interval are consistent with a cenobamate withdrawal effect. The terms most likely to have a causal relationship are “insomnia”, “anxiety”, “depressed mood”, “nightmare”, “decreased appetite”, “tremor”, “body temperature increased”, “chills”, “heart rate increased”, “nervousness”, “nightmare”, and “tachycardia”.

8.6. Analysis of Submission-Specific Safety Issues

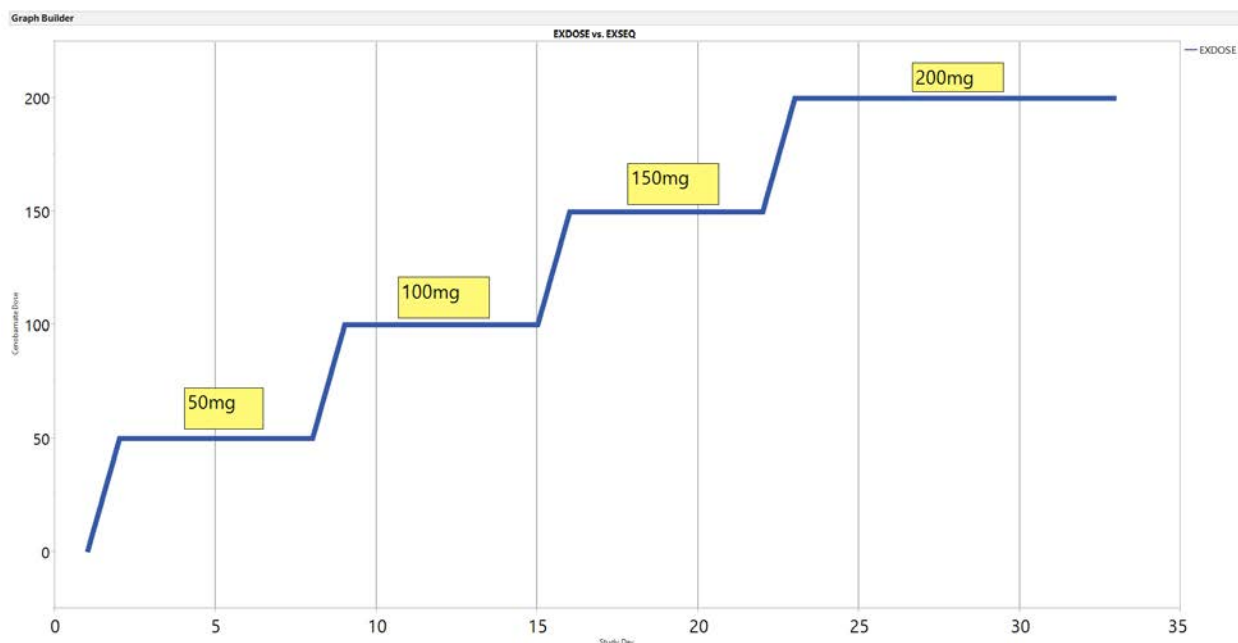
8.6.1. DRESS Risk

DRESS Cases (3)

C020 (TQT study) Subject YKP3089C020-(b) (6)

Study C020 was the TQT study in healthy volunteers. Subject (b) (6) was a 38 yo female who developed a rash on her face and neck with pruritis on study day 32 while taking 200mg of cenobamate. Study drug was discontinued on day 33. The subject was initially treated with diphenhydramine 25mg to 50mg up to three times a day. The subject reported several adverse events in the days and weeks after discontinuation from the study including, including depressed mood, face swelling, anxiety, back pain, alopecia, ecchymosis, blurred vision, chest pain, dyspnea, palpitations, headache, cough, fatigue, and asthenia. The depressed mood AE began 7 days after the last dose of study drug and the PI considered it possibly related to study drug. A text review of the course of events is presented in the following paragraphs. See [Figure 77](#) for cenobamate exposure by study day. See [Figure 78](#), [Figure 79](#) and [Figure 80](#) for a graphic overview of laboratory events by study day as well as the start of prednisone tape and day of death.

Figure 77 C020, Subject (b) (6) Cenobamate Dose by Study Day



Abnormal laboratory findings at the early termination event on (b) (6) (Day 33) included: alanine aminotransferase (ALT) 107 U/L (reference range: 10 - 60 U/L), aspartate aminotransferase (AST) 64 U/L (reference range: 14 - 47 U/L), basophil percentage 1.5% (reference range: 0 - 0.7%), monocytes 12.4% (reference range: 3.9 - 11.5%), and absolute neutrophils 1.8 thou/ μ L (reference range 1.9 - 7.9 thou/ μ L). Vital signs and ECG parameters were within normal limits at the early termination event.

On study day 39 the subject returned to clinic and the rash was noted to be worse; a generalized maculopapular rash was now covering her face, neck, and trunk, anterior and posterior down to buttocks. The subject complained of pruritus and reported the diphenhydramine was not helping. In addition, she reported difficulty breathing and felt the need to cough to breathe better. She also reported flank pain and nausea. The subject was referred to a local emergency department.

Upon presentation to the emergency room the subject reported acute non-radiating back pain (right mid and right low back). The subject was alert and oriented. Vital signs taken in the emergency department showed blood pressures ranging from 91/58 to 98/62 mmHg, pulse rates of 93 to 104 bpm, temperature of 100.0°F, and oxygen saturation percentages of 96% to 98% on room air. The subject was sent home from the emergency room with instructions to follow up in 2 to 3 days.

She then returned to the clinic on study day 40 and reported no improvement in the rash or pruritus and had continued nausea. The ALT and AST continued to increase along with ALP, bilirubin, GGT and LDH.

On Study day 42 the subject had continued macular rash on chest, abdomen, back and legs with continued nausea. The subject had a dermatology assessment and the rash was noted to be diffuse, was itchy and red. She felt better after prednisone. A punch biopsy was performed, and the results were consistent with DRESS syndrome. The subject was continued on prednisone 20mg daily. On study day 44 the subject returned to clinic and the generalized erythropapular rash was worse and pronounced diffuse adenopathy was noted. The subject felt generally ill. Hepatic enzyme studies continued to worsen. Her ALT (937 I/U) and AST (610 I/U) were continuing to increase. Coagulation parameters were obtained and showed an elevated prothrombin time (PT, 13.5 seconds; reference range: 9.6 - 11.6 seconds) and international normalized ratio (INR, 1.3; reference range: 0.9 - 1.1). The subject then returned to the emergency room. The subject was followed by an internal medicine doctor and a hepatologist. While hospitalized, the subject continued receiving prednisone 60 mg and triamcinolone cream, hydroxyzine 25 mg, hydrocortisone cream, and diphenhydramine cream. She had a liver duplex ultrasound that was normal. Vital signs included blood pressures of 85 - 105/58 - 75 mmHg, pulse rates of 70s to 90s bpm, respiratory rate of 16 rpm, temperatures ranging from 36.7 to 38.1°C, and oxygen saturation of 94% on room air.

The subject's ALT and AST increased further while hospitalized, with maximum ALT of 1327 U/L and AST of 865 U/L on (b) (6) (Day 46). In addition to the elevated transaminases and out-of-range blood count differential parameters during the hospitalization, the subject's hemoglobin and hematocrit values were low, with hemoglobin values ranging from 10.9 to 11.8 g/dL (hospital reference range: 12.0 - 15.5 g/dL) and hematocrit values ranging from 32.7% to 34.7% (hospital reference range: 34.9% - 44.5%).

She was discharged to home on study day 46, with prescriptions for prednisone 60 mg with taper over the next 2 weeks, hydroxyzine 25 mg, triamcinolone cream, and diphenhydramine cream. On study day 49 the subject returned to clinic and hepatic enzymes remained elevated but were trending downward. The subject reported that the pruritus and rash were still present and follow up coagulation studies were within normal limits.

On study day 50 at a hepatology follow up visit the rash was dramatically improved. Hepatic enzymes were improving. Treatment at the time included prednisone 20mg daily but there were instructions to taper over 2 weeks. On study day 52 the subject returned to clinic. Lymphadenopathy was still present notably along the right posterior cervical area. She reported the swelling was improving. Hepatic enzyme elevation continued with ALT (1000 I/U) and AST (575 I/U).

On study Day 64, the subject returned to the clinic and reported the rash was improved but noted that sometimes it returned then went away. She also reported that since study day 57, she noticed facial swelling in the middle of her face and lips, which was worse upon waking in the morning. It had been progressively getting more noticeable and she reported that now the inside of her mouth was swollen. She denied shortness of breath or difficulty breathing.

Upon examination, her face and oral mucosa were noticeably swollen, and her swollen posterior cervical lymph node remained enlarged. The following day the subject noted that the rash was more noticeable and red. On study day 68 the subject returned to clinic and was noted to have continued facial swelling, and a generalized maculopapular rash involving the trunk, neck, bilateral arms, and upper legs. The subject was started on a new course of prednisone. The subject reported feeling sad.

On study day 72 the subject was contacted by phone and reported that the rash, facial swelling, pruritus, and feeling sad continued with no improvement from yesterday. On study day 76, the clinic staff spoke to the subject on the phone. The subject stated that the facial edema and rash were now minimal, and that she was feeling less sad. On study day 80, the subject was contacted by phone and stated that she still had facial edema and was having feelings of sadness. She was concerned about losing so much hair. She stated she took her last dose of prednisone.

On study day 81, the subject was initially contacted by phone and stated she was having chest pain since the day before. The subject returned to the clinic, and reported chest pain with radiation to her back, that was accompanied by shortness of breath, palpitations, and blurred vision. The chest pain was still present but improved at the visit, and she was still having palpitations and mild shortness of breath. The subject also stated she was going to an emergency room after the clinic visit. Later that day, the clinic contacted the subject by phone and the subject stated her chest pain improved so she did not go to the emergency room. The clinic staff advised the subject to go to the emergency room, but she stated she would go if the chest pain worsened but she did not want to go at that time.

On study day 83, the subject returned to the clinic. Overall, her physical examination was much improved. She was noted to have mild edema to her cheeks and periorbital areas, and minimal rash to her bilateral forearms. The subject stated that she had increased stressors in her home life and finances over the past few days. The chest pain was better at the time of the visit, but she still noted some intermittent chest pain with exertion. She also reported a recent onset of fatigue. Vital signs included a blood pressure of 94/65 mmHg and pulse rate of 83 bpm. An ECG was within normal range, including a QTcF interval of 397 msec. Her liver enzymes were within normal range (ALT 43 I/U and AST 43 I/U), however, several WBC differential parameters were still elevated, including a WBC count of 11.3 thou/ μ L and eosinophil percentage of 13.7%.

On study day 86, Subject (b) (6) called into the clinic and reported ongoing chest pain. She stated that the chest pain was worse with movement. She denied shortness of breath but did state her chest hurt when she took a deep breath. She also reported ongoing stress with regard to family finances and the need to find childcare for her return visits. The subject was reminded again to go to the emergency room for chest pain. The clinic staff suggested the subject try some relaxation techniques, such as taking a warm bath or listening to music. Later that evening she complained of chest pain to her husband, but it subsided.

On study day 87, the subject was found unresponsive by her husband and emergency medical services (EMS) were notified. She was transported to a local emergency room where she was pronounced dead. On [REDACTED] a post-mortem examination was performed. The autopsy findings concluded that Subject [REDACTED] died from a cardiac dysrhythmia due to eosinophilic myocarditis due to DRESS, with findings of pleural effusions, pericardial effusion, pulmonary edema, cardiomyopathy, and necrotizing myocarditis.

Figure 78 C020 Subject [REDACTED], Profile of ALT and Total Bilirubin by Study Day

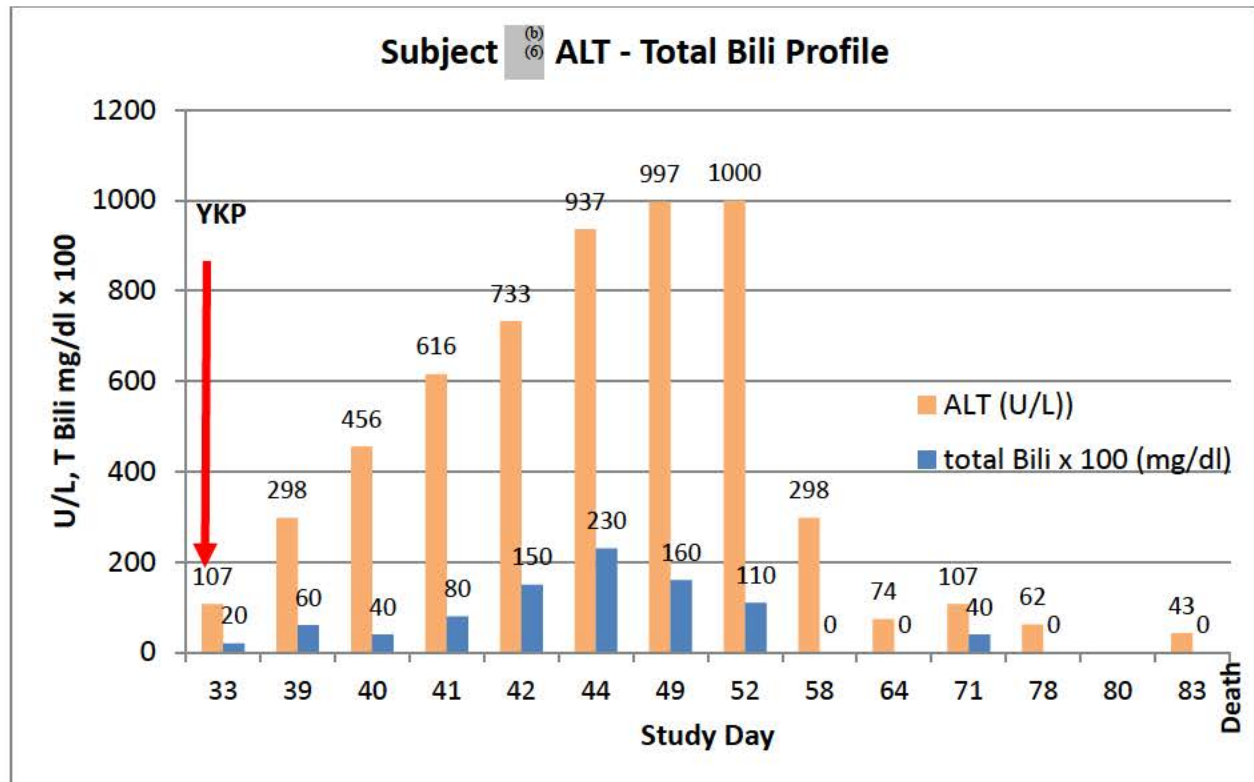


Figure 79 C020 Subject (b) (6) Eosinophil Percent by Study Day with Key Intervention Milestones

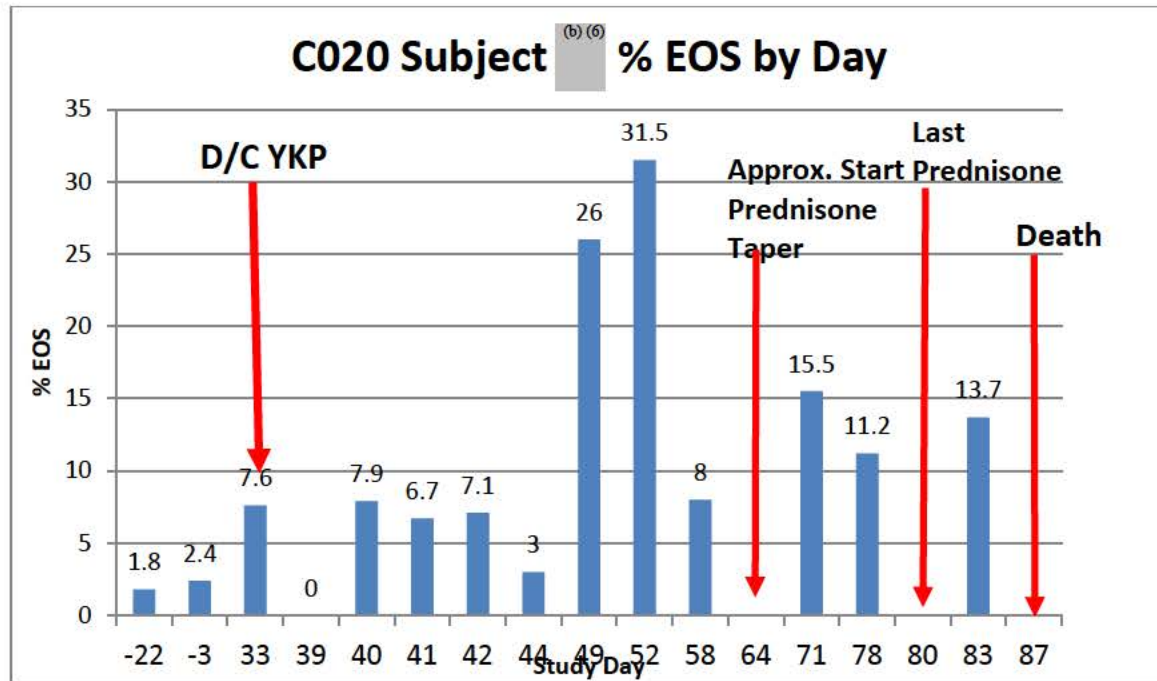
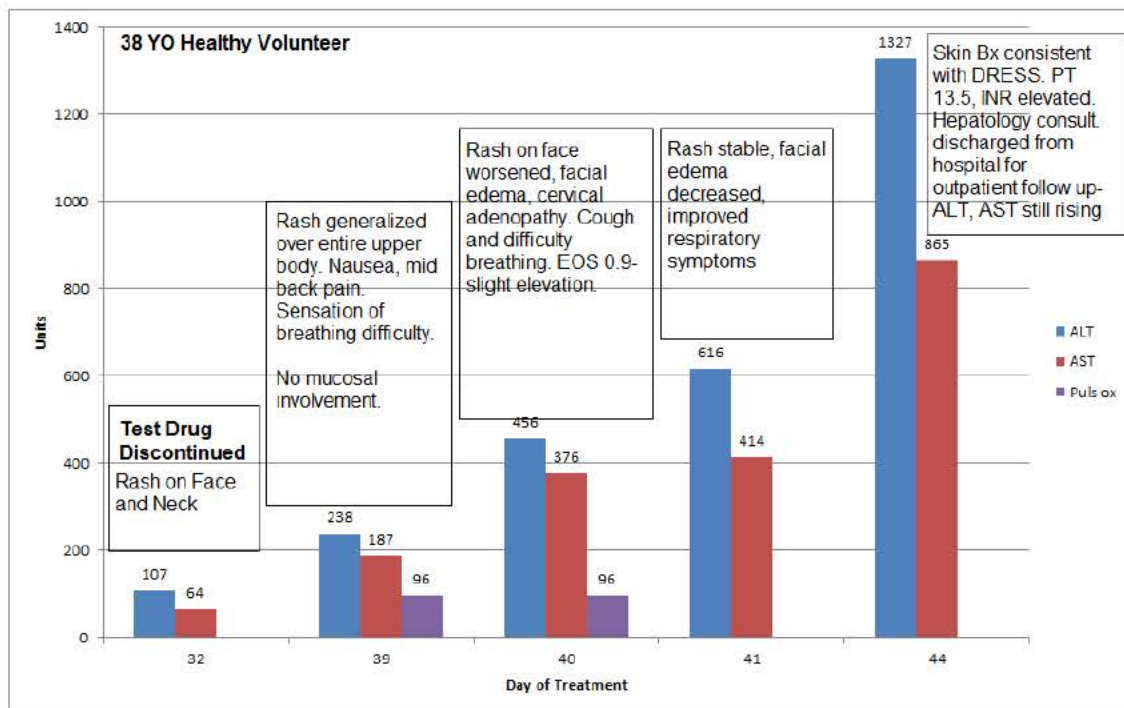


Figure 80 C020, Patient YKP3089C020- (b) (6) Clinical Course in Alignment with Clinical Laboratory Measures of ALT and AST with Pulse Oximetry

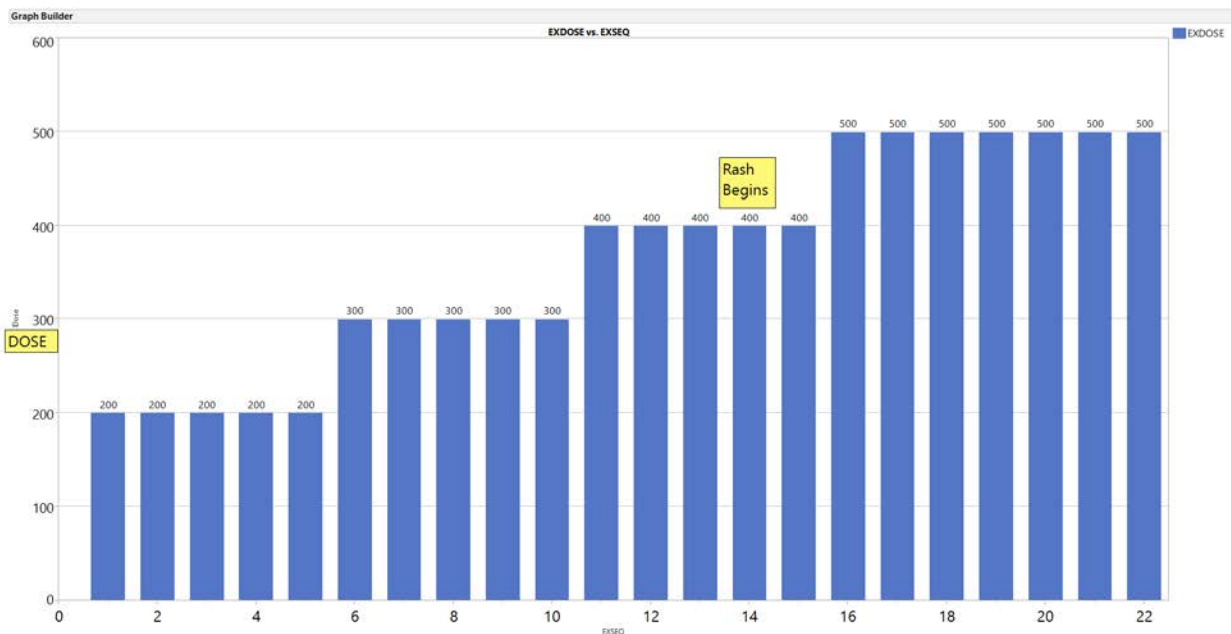


C018 (PK-Titration, MAD study) Subject YKP3089C018- (b) (6)

Subject (b) (6) was a 50 yo male who began to experience warmth to the trunk and developed a diffuse erythematous rash to the trunk, arms, and legs (bilaterally) on Day 14, approximately 5.4 hours after receiving the 4th dose of 400 mg of cenobamate.

On Study Day 22, the rash was noted to include the palms of the hand and soles of the feet. No stridor was noted, and there was no uvular or tongue swelling; the subject denied difficulty swallowing and was allowed to dose. Later that same day, the subject began to complain of tightness of facial skin and was noted to have soft facial tissue swelling as well as swelling of the digits bilaterally. No swelling of the lips or oral mucosa was noted. At this point the decision was made by the PI to discontinue dosing and keep the subject domiciled in the clinic for safety. The subject received the last dose of 500 mg cenobamate on Day 22. The subject received a total of 5 doses each of 200, 300, and 400 mg of cenobamate and 7 doses of 500 mg cenobamate before the study drug was discontinued, Figure 81.

Figure 81 C018, Subject (b) (6) DRESS: Cenobamate Dose by Study Day and Start of Rash (Day 14)



On Day 23 in the morning, the subject had increased weakness; stating that it was difficult to get out of bed. The rash remained present and the subject continued to deny any difficulty breathing or swallowing. That afternoon, he began to have swelling of the lips and bilateral eyelids, body aches, and a burning sensation in the areas covered by the rash. Vital signs were normal with the exception of a pulse rate of 99 bpm at a single time point. That evening, his oral temperature increased to 103.8°F, accompanied by a pulse rate of 106 bpm.

On Day 24, the subject again had an increased temperature, with a maximum of 103.2°F, and increased heart rate of 106 bpm. He received oral diphenhydramine and paracetamol. The

pruritic rash was still present. He had continued weakness with observed difficulty changing positions in bed. He reported feeling achy all over, with moderate pain to entire body. He also was noted to have generalized pustules over his face and increased swelling to the facial soft tissues. The subject was given intramuscular methylprednisolone sodium succinate. The patient was transferred from study site to a local emergency room.

Within 24 hours of hospitalization, the patient showed signs of clinical improvement with less fever, feeling stronger and some resolution of the rash. Renal function improved, WBC counts reduced with normalization of granulocytes and calcium increased. Hepatitis panel for A, B and C was negative. However, on study day 27, AST increased to 568 U/L, ALT increased to 809 U/L and alkaline phosphatase increased to 133 U/L.

On study day 26, a dermatologist reported a diffuse dusky discoloration of skin involving hands and feet plus areas of fine scaling and palpable purpura extensive on legs. His first impression was drug hypersensitivity syndrome including systemic symptoms and leukocytoclastic vasculitis. A CBC with differential ordered by the dermatologist revealed eosinophils of 11% with a total WBC of 7.1 Thou/ μ L. Based on the elevated eosinophil count, the dermatologist believes the condition of the subject can best be characterized as a DRESS syndrome. By study day 31 the rash was resolving, and the liver and kidney functions tests were returning towards normal.

By study day 49 laboratory studies revealed that GGT and ALT were only slightly elevated. The symptoms of itching and rash continued to improve per follow-up phone calls by the subject. The SAE was considered resolved on study day 74.

C017 DB, Patient YKP3089C017- (b) (6)

This case is also presented in Section 8.4.4 as a discontinuation from study C017, see [DRESS Case, study C017](#).

This patient was a 36 yo female who presented to the emergency room on study day 24 after several days of fever and chills, a 2-day history of diffuse macular erythematous and pruritic rash covering the majority of her body surface area including the face trunk, back, arms, and legs. The patient also had arthralgia, myalgia and memory problems. The cenobamate dose was scheduled to be 200mg starting 15 days prior to the event. The drug accountability record reveals no study drug was taken from (b) (6) to (b) (6) Study day 1 was (b) (6) On admission to the hospital the patient had a temperature of 101.3 F and a morbilliform rash on the abdomen and legs. A dermatology consultant made the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome.

A CT scan of the chest and pelvis was performed on study day 29 to evaluate for lymphoma. Findings included bilateral pleural effusion, right side was greater than the left side, with right

lower lobe consolidation. A moderate amount of free fluid in the abdomen and pelvis tracking along the right pericolic gutter was observed, with either a thickened gallbladder wall versus fluid in the gallbladder fossa. Mediastinal lymph nodes were enlarged bilaterally but not consistent with lymphoma along with bilateral axillary and inguinal lymph nodes. Treatment for the event included paracetamol (650 mg, oral, every 6 hours), diphenhydramine hydrochloride (25 mg, oral, QD; 50 mg, oral, QD), glucose (50 mL, IV, once), lidocaine (1 mL/day, infiltration, once), sodium chloride (1000 mL, IV, PRN), and prednisone (60 mg, oral, QD). The subject was treated with methylprednisolone (60 mg, IV, every 8 hours) before being transitioned to prednisone

Table 95 C017, Patient YKP3089C017- (b) (6) Laboratory Values from Hospitalization by Study

Test Name (Unit)	Result	Normal Range	Study day
Alanine aminotransferase (not reported)	81	Not reported	24
Aspartate aminotransferase (not reported)	54	Not reported	24
Eosinophil percentage (%)	13.6	Not reported	24
Hemoglobin (not reported)	13.3	Not reported	24
Lymphocyte percentage (%)	16.6	Not reported	24
Neutrophil percentage (%)	59	Not reported	24
Platelet count (not reported)	142,000	Not reported	24
Sodium (not reported)	132	Not reported	24
White blood cell count (not reported)	4.0	Not reported	24
White blood cell count (not reported)	3.8	Not reported	27
Alanine aminotransferase (not reported)	158	Not reported	28

On study day 31, the subject was discharged from the hospital. According to the investigator, the subject went to an emergency room on study day 35 and study day 38 because of rash. Following this, the subject was lost to follow up despite multiple attempts to have her return. The outcome of the event of DRESS syndrome was unknown.

Reviewer Summary, DRESS Cases:

Subject YKP3089C020- (b) (6) developed the first hypersensitivity features on day 10 of 200mg/day dosing in a program with weekly escalation in 50mg increments. The second subject that develop DRESS, (YKP3089C018- (b) (6)) developed first DRESS features on day 4 of 400mg/day dosing after a total of 14 days of exposure to cenobamate. The precise dose and

exposure in the third case (YKP3089C017- (b) (6)) is not as clear. The patient was scheduled to be on 200mg for 15 days at time of first hypersensitivity features after treatment for a total of 23 days.

In cases YKP3089C020- (b) (6) and YKP3089C017- (b) (6) the titration schedules were similar, starting at 50mg and escalating by 50mg weekly. Case YKP3089C018- (b) (6) had the most rapid dose escalation starting at 100mg and advancing by 100mg weekly. All are more rapid than proposed dosing that begins at 12.5mg for two weeks before advancing to 25mg for two weeks.

In cases YKP3089C017- (b) (6) and YKP3089C018- (b) (6) the emergence of DRESS features was more immediate while in case YKP3089C020- (b) (6) there was a one-week interval of mild expression of DRESS. All three patients received corticosteroid therapy with clinical benefit noted. Subject YKP3089C020- (b) (6) appears to have a degree of relapse as prednisone was being tapered. A potential difference between the fatal case of DRESS (YKP3089C020- (b) (6)) and the other cases was the duration of cenobamate treatment. Case (b) (6) was treated for 32 days compared to 14 days and 23 days in the cases that resolved.

[DNP Safety Review, Dress](#)

A dedicated safety review of the DRESS risk and Study C021 was performed by the internal DNP safety reviewer.¹⁹ This review includes an assessment of the DRESS cases presented in the prior section. The reviewer concludes that though no additional DRESS cases were identified in study C021 but the data do not allow a definitive conclusion that the reduced cenobamate titration rate is solely responsible for the observed reduction in DRESS risk. This is because there were demographic differences between the Phase 1 trial that were the source of 2 of 3 DRESS cases as well as differences in exclusion criteria and pharmacovigilance measures employed across C021 and the earlier studies.

The safety reviewer concluded that a Medication Guide should be included with labeling that includes information like that provided to patients in study 021 about signs and symptoms of DRESS and instructions to contact health care providers immediately if these occur. The sponsor should closely monitor for and include as 15-day reports to the Agency any spontaneous reports suggestive of DRESS with the intention of assessing real world use risk and identification of predictive factors. In addition, the sponsor should perform genomic studies to look for predictive factors for DRESS. Also, the warning for DRESS in Section 5 of labeling should not imply that DRESS risk has been eliminated with the use of a lower starting dose and slower titration schedule.

¹⁹ Gerard Boehm, ODE 1, DNP, 9/12/19:

https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80515183&_afRedirect=395963667581783

C021 Hypersensitivity Reports

The first patient was screened for study C021 on (b) (6) but IND 76809 (YKP) was placed on partial clinical hold on 11/25/15 due to DRESS risk. Conditions of the partial hold did not allow new patient recruitment. Thereafter study C021 was modified to assess safety and DRESS risk using a titration schedule with reduced dose escalation rate, [Table 96](#). The sample size was also expanded to cap the DRESS risk with the upper limit of the 95% confidence interval of 0.3% (given 0 as the point estimate of new DRESS cases). A continue partial hold letter was sent on 2/26/16 allowing conditional new patient recruitment. The conditions limited cenobamate dose to 200mg, an expansion of the already planned safety study C021 was required to “provide an adequate number of patients exposed for a minimum of six months to cap the risk of DRESS to a level acceptable for the proposed indication”. In addition, a monthly hypersensitivity report to include any hypersensitivity reactions reported by investigators, whether serious or not, was required to be submitted.

Table 96 Study C021, Cenobamate Titration Schedule

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Dose mg cenobamate	12.5	12.5	25	25	50	50	100	100	150	150	200	200	250	250	300	350	350	400

Over a period of 26 months the hypersensitivity reports captured 66 cases. From among these 66 cases there were 9 SAEs with no suspected or confirmed DRESS reports identified by the sponsor. These reports were monitored by the clinical reviewer over the 26 months of submissions and is in agreement with the conclusions regarding DRESS cases.

Relevant reports concerning hypersensitivity are captured in previous sections on [SAEs](#), [Dropouts and Discontinuations](#) and [TEAEs in study C021](#).

Rapid Onset Hypersensitivity Events

C021

Patient YKP3089C021- (b) (6)
Day 2, 12.5mg

A 46 yo female developed a moderate urticarial body rash after two doses of 12.5mg cenobamate. The rash was assessed as an SAE (also noted above in SAE). No additional physical or clinical laboratory evidence of hypersensitivity was present on evaluation. The subject recovered within 1 day.

Patient YKP3089C021- (b) (6)

Day 3, 12.5mg

A 32-year-old male developed lip swelling on the third morning after starting cenobamate 12.5mg. The patient went to the emergency room. No lymphadenopathy, respiratory or other signs of hypersensitivity were present. The patient recovered from the event in 24 hours.

Phase 1 Studies

YKP3089C016- (b) (6) SAE- PT Nausea:
Day 1, 200mg

She began dosing with phenytoin 300 mg/day on (b) (6). On (b) (6) 200 mg/day of YKP3089 was added to the regimen. Both drugs were given at 8 PM daily. On (b) (6) (b) (6) *less than 4 hours after the first dose of YKP3089, she complained of numbness of the tongue.* On (b) (6) she was found to have a macular rash on the lower extremities and painful papules on the tip of her tongue (preferred term: glossitis). On (b) (6) (b) (6) she complained of tingling of the tongue (oral hypoesthesia). The last dose of YKP3089 and phenytoin was given on (b) (6). On (b) (6) she developed elevated temperature (pyrexia), dizziness, mucositis (glossitis), and blisters on the anterior one inch of the tongue and on the buccal mucosa one inch in from the lips. Her lips were swollen and painful. On (b) (6) she received acetaminophen for pyrexia (her temperature rose to 104.6° F). On (b) (6) she was found to have a fine light macular rash in a glove and stocking distribution. She also complained of abdominal discomfort, nausea, body aches (pain), and anxiety. On (b) (6) she received oral acetaminophen, oral diphenhydramine, intravenous normal saline, and lidocaine oral rinse. On the evening of (b) (6) (b) (6) (Day 6 of Study Period 2), her nausea and abdominal pain worsened, her temperature remained elevated, and the patient was transferred to a nearby hospital emergency room.

In the emergency room, Subject (b) (6) was given oral Tylenol® 1000 mg, intravenous normal saline, intravenous vancomycin 1-gram, intravenous ceftazidime 1 gram, and intravenous Solu Medrol® 125 mg. After several hours, the subject was admitted as an inpatient with suspected Stevens- Johnson Syndrome, drug reaction, and tachycardia. On admission to the hospital her temperature was 101.7°F. Various physicians reported whitish plaques and ulcerations on the tip of the tongue and just inside the lips on the buccal mucosa. A fine diffuse macular rash was seen at times on the arms, legs, and torso. Other relevant findings included normal conjunctiva, no lymphadenopathy, and no raised lesions or blisters on the skin. She improved steadily after admission and all treatments were stopped on (b) (6). Her oral lesions were almost completely resolved by the time of discharge. All baseline laboratory results were within normal limits.

Subject (b) (6) was discharged to home on (b) (6) (Day 10) with a Solu-Medrol® DosePak and orders to recheck laboratory values. The subject returned to the Celerion clinic after discharge from the hospital and again on (b) (6). All AEs, with the exception the

macular rash and the elevated liver enzyme AEs, were resolved prior to discharge from the hospital. The macular rash AEs were resolved by Day 20 (b) (6)

YKP3089C018- (b) (6) PT Drug Hypersensitivity
Day 1, 200mg

A 34 yo male subject was discontinued from the study because of a drug hypersensitivity reaction that began on Day 1, 7.8 hours after dosing with *200 mg YKP3089*. The subject received 1 dose of 200 mg YKP3089 before dosing was discontinued.

On Day 1 (b) (6) the subject reported laying down to sleep after lunch and upon awakening noted erythema to his trunk, bilateral swelling of the eyelids, and a tight feeling in the face. He denied any welts or pruritus. Physical examination revealed no swelling of the uvula or tongue, and lungs were clear to auscultation. Later that evening, the subject reported feeling worse and the edema was increased. The subject was administered oral diphenhydramine.

On Day 2 (b) (6) during the night, the erythema to chest was more pronounced and the eyelid edema had increased. In the morning, redness was noted on bilateral legs. The subject denied any pain or pruritus. He was able to open eyes and denied any difficulty swallowing or breathing. The subject was again administered oral diphenhydramine. Vital signs remained stable. Medical assessment by the PI revealed a "diffuse confluent macular rash without papules, pustules or bullae involving predominantly the trunk and proximal extremities sparing mucosal sites, palms and soles." The rash had been noted by the subject to have progressed over the previous several hours. The PI decided not to administer any more doses of study drug. He denied pruritus and dyspnea and remained afebrile. The PI ordered oral diphenhydramine every 6 hours as well as a methylprednisolone tapering dose. Safety vital signs were also ordered to be done twice daily. These remained within normal limits. The subject remained confined at the clinic for continued assessment. Blood and urine tests done at this time to check for eosinophilia and kidney or liver involvement were all negative.

On Day 3 (b) (6) the facial swelling was resolved, and edema of the eye lids was significantly decreased. The diphenhydramine was discontinued as were the safety vital signs. Erythema of the bilateral legs was resolved. On Day 4 (b) (6) the subject was discharged from the clinic with orders to continue the methylprednisolone tapering dose and to call the clinic with any change in condition. At the early termination physical, the subject was noted to have slight erythema on legs as well as residual erythema to the bilateral eyelids.

Follow up phone calls were made with the subject to track the resolution of the AE. The erythema of the eyelids, trunk and legs as well as the edema of the eyelids continued to improve. On Day 8 (b) (6) the subject reported that the erythema of the legs had resolved. On Day 10 (b) (6) the subject reported that the erythema and edema of

the eye lids had resolved. The AE was considered resolved on Day 10. The PI considered this AE to be probably related to the study drug.

Measures to Reduce DRESS Frequency

Reduction of the rate of dose escalation and vigorous pharmacovigilance have been the approach to mitigate risk of DRESS. There is evidence in nonclinical model and also evidence from this approach in the clinical use of lamotrigine for support of slow titration in the reduction of hypersensitivity reactions.

In a nonclinical model of penicillamine induced autoimmunity a dose of 10mg/day for 2 weeks was shown to induce immune tolerance. In addition, the tolerance could be transferred to a naïve animal with spleen cell transfer.²⁰ Clinical support for a strategy of dose reduction is found in experience with lamotrigine. In January 1994, the recommended starting dose of lamotrigine was lowered in an attempt to reduce the incidence of rash. After the starting dose was reduced. The incidence of serious rash was significantly reduced; however, no corresponding reduction in the overall incidence of lamotrigine-related skin rash was observed.²¹

DRESS Risk in Prospective

DRESS has been observed across several categories of therapeutic intervention in addition to Antiepilepsy drugs. Medications most commonly associated with DRESS syndrome in addition to AEDs are antibiotics (particularly beta-lactams), and allopurinol. Other medications that are known to be associated with DRESS include non-steroidal anti-inflammatory drugs, captopril, mood stabilizers, and antiretroviral drugs.

A search using the “FDALabel” tool for the occurrence of DRESS in Section 5 identifies 9 approved AEDs. In eight of the nine products there is a standard language heading within section five for the DRESS warning entry, shown in [Table 97](#).

Table 97 AED’s where DRESS appears in W & P, Section 5 of Labeling

Trade Name	Dedicated Section 5	Including Multiorgan hypersensitivity	Location non-PLR	Standard Section 5 Heading*
TRILEPTAL	y	MOH		Y
APTIO M	Y	MOH		Y
BANZEL	Y	MOH		Y
TEGRETOL	Y	MOH	Warnings	Y

²⁰ Masson MJ and Uetrecht JP. Tolerance Induced by Low Dose d-Penicillamine in the Brown Norway Rat Model of Drug-Induced Autoimmunity Is Immune-Mediated. *Chem. Res. Toxicol.* 2004, 17, 82-94.

²¹ Wong ICK, Mawer GE, Sander J. Factors influencing the incidence of lamotrigine-related skin rash. *Annals of Pharmacotherapy* 1999; 33(10): 1037-42

DEPAKOTE	Y	MOH		Y
DILANTIN 125	Y	MOH		Y
FYCOMPA	Y	MOH		Y
LAMICTAL	N	MOH		No, included in primary MOH text
NEURONTIN	Y	MOH		Y
VIMPAT	Y	MOH		Y
*Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity				

The full list of drugs with DRESS appearing in Section 5 identifies 45 agents by generic name excluding the AEDs identified in [Table 97](#). This list includes antibiotics, antipsychotic, radiocontrast agents, and antiretroviral drugs.

Table 98 Drugs (generic names) Where DRESS Appears in Section 5 of Labeling

Generic)
AMIFOSTINE
ARMODAFINIL
ATAZANAVIR
ATAZANAVIR AND COBICISTAT
AZITHROMYCIN
AZITHROMYCIN DIHYDRATE
BENDAMUSTINE HYDROCHLORIDE
BENZNIDAZOLE
BISMUTH SUBCITRATE POTASSIUM, METRONIDAZOLE, TETRACYCLINE HYDROCHLORIDE
CELECOXIB
CLINDAMYCIN PHOSPHATE
CLOZAPINE
DARUNAVIR, COBICISTAT, EMTRICITABINE, AND TENOFOVIR ALAFENAMIDE
DEFERASIROX
DOLUTEGRAVIR SODIUM AND RILPIVIRINE HYDROCHLORIDE
DOXYCYCLINE HYCLATE
DUVELISIB
EMTRICITABINE, RILPIVIRINE HYDROCHLORIDE, AND TENOFOVIR ALAFENAMIDE
EMTRICITABINE, RILPIVIRINE HYDROCHLORIDE, AND TENOFOVIR DISOPROXIL FUMARATE
ETRAVIRINE
FEBUXOSTAT
FENOFIBRATE
FENOFIBRIC ACID
IODIXANOL
IOHEXOL
IOPROMIDE
IOVERSOL
LEFLUNOMIDE
LENALIDOMIDE
MARAVIROC
MEROPENEM
MINOCYCLINE HYDROCHLORIDE
MODAFINIL
OLANZAPINE
OLANZAPINE AND FLUOXETINE HYDROCHLORIDE

OLANZAPINE PAMOATE
POMALIDOMIDE
RILPIVIRINE HYDROCHLORIDE
TERIFLUNOMIDE
THALIDOMIDE
VEMURAFENIB
ZIPRASIDONE HYDROCHLORIDE
ZIPRASIDONE HYDROCHLORIDE; ZIPRASIDONE MESYLATE
ZIPRASIDONE MESYLATE

An analysis using Empirica Signal is performed to identify drugs that have associations with DRESS. This analysis reveals 134 generic active moieties with an EB05 > 5 where 2 is considered a potential safety signal. When sorted for maximum EB05 and number of cases there are 49 moieties with greater than 100 case entries and an EB05 > 2. This list is shown in [Table 99](#).

Table 99 Disproportionality Analysis for DRESS: Any Active Moiety Search Term Pair with Number of Report Entries (n) and EB05 (Empirica Signal)

Single active moiety (SAM)	n	EB05	Single active moiety (SAM)	n	EB05
ALLOPURINOL	1920	122.24	METRONIDAZOLE	239	8.59
DAPSONE	195	55.21	VEMURAFENIB	119	8.44
RIFAMPIN	706	39.57	CLINDAMYCIN	178	8.25
ETHAMBUTOL	363	38.01	CIPROFLOXACIN	386	7.52
VANCOMYCIN	1292	37.70	RALTEGRAVIR	107	6.85
PYRAZINAMIDE	358	36.24	ACYCLOVIR	178	6.52
ISONIAZID	454	31.58	DOXYCYCLINE	128	6.39
CEFOTAXIME	128	30.46	LEVETIRACETAM	410	6.14
ZONISAMIDE	189	26.95	FLUCONAZOLE	112	5.90
PHENOBARBITAL	266	26.15	TELAPREVIR	340	5.89
CARBAMAZEPINE	984	25.70	LEVOFLOXACIN	291	5.56
PIPERACILLIN	465	25.65	VALPROATE SODIUM	141	5.55
TAZOBACTAM	448	24.17	VALPROIC ACID	295	5.48
MINOCYCLINE	239	23.32	LINEZOLID	103	5.19
PHENYTOIN	666	22.16	ABACAVIR	108	5.09
SULFASALAZINE	361	20.87	FUROSEMIDE	175	4.26
LAMOTRIGINE	1390	19.48	ENOXAPARIN	118	4.17
SULFAMETHOXAZOLE	656	18.38	AZITHROMYCIN	111	3.80
CEFTRIAZONE	454	18.34	DICLOFENAC	183	3.72
TRIMETHOPRIM	662	17.40	AZATHIOPRINE	107	3.32
MEROPENEM	211	17.26	PANTOPRAZOLE	198	3.15
CLAVULANIC ACID	145	16.14	PEGINTERFERON ALFA-2A	199	3.08
GENTAMICIN	113	14.39	LAMIVUDINE	111	2.35
AMOXICILLIN	818	14.31	RIBAVIRIN	248	2.35
CLAVULANATE POTASSIUM	232	9.96			

Reviewer Comment, DRESS Risk

The three cases of DRESS identify threat of a serious adverse event. In addition, the reports of early and intense hypersensitivity reactions reveal a propensity to dysfunctional immune system activation. However, it is not certain if the events identified in the section “Rapid Onset

Hypersensitivity Events” have the same mechanistic drivers as those underlying progression to DRESS syndrome or whether those hypersensitivity events forecast DRESS.

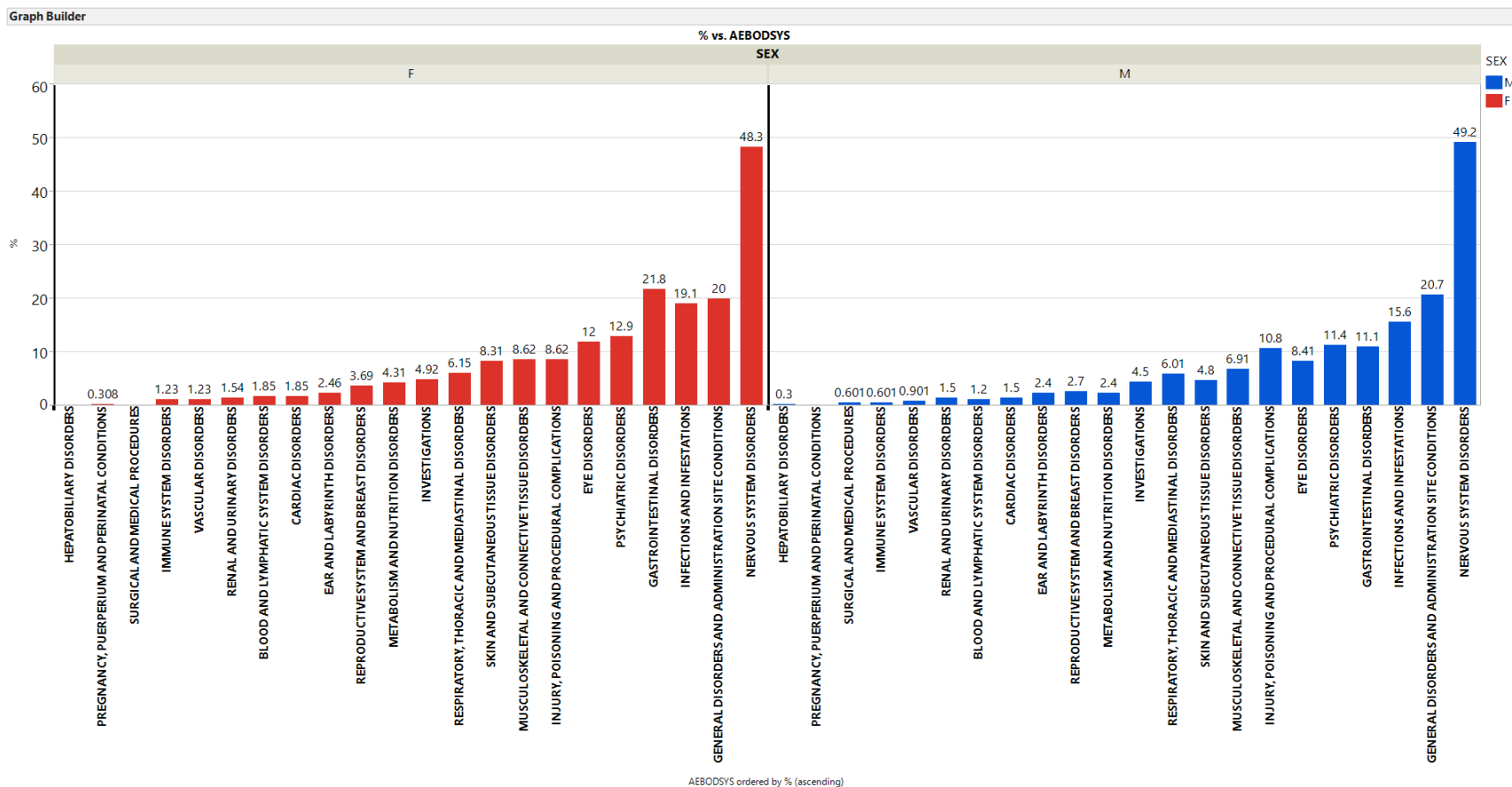
No additional DRESS cases occurred with the reduced titration rate in study C021. The study does not prove the strategy of slow escalation alone eliminates DRESS risk due to a specific mechanism, such as development of immune tolerance. However, the methodology of reduced titration and early identification of hypersensitivity signs and symptoms were successful in the study population and the outcome supports a risk level that is in alignment with a similar threat from SJS/TENS in lamotrigine. In addition, as shown in [Table 98](#) and [Table 99](#), this serious adverse event is present and managed in current mainstream AEDs and drug treatments in other therapeutic areas. As expressed in the safety review, labeling should include a medication Guide to provide patients with the same warning information on DRESS presentation.

8.7. Safety Analyses by Demographic Subgroups

C013-C017 Pool

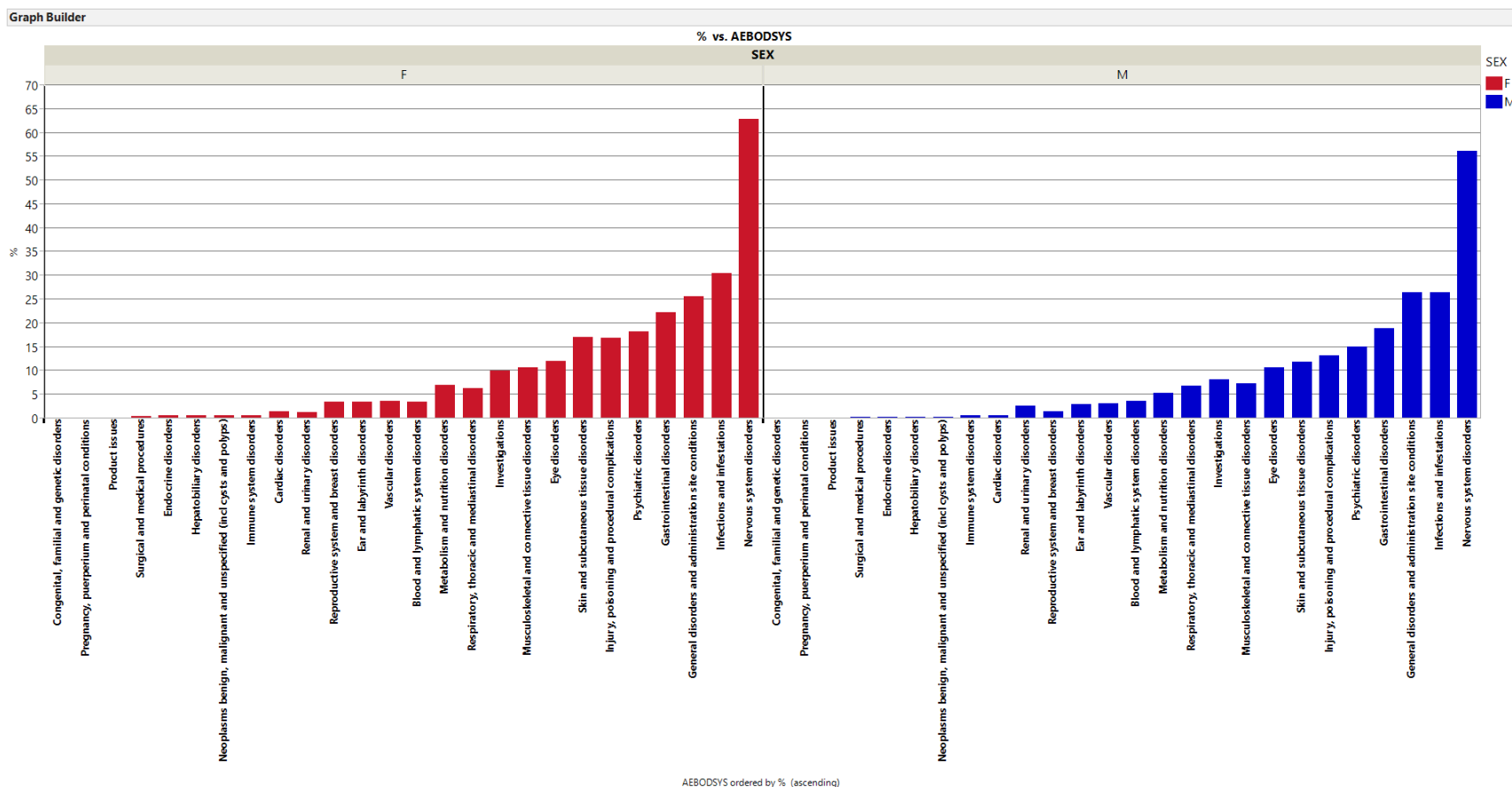
Examination of the distribution of the frequency of adverse events by SOC in males and females reveals the most notable difference occurs in the SOC “Gastrointestinal Disorders” where there is an excess of 10.1% in the proportion of females over males. In the remaining SOCs the differences are small and unlikely to represent a substantive clinical difference.

Figure 82 C013-C017 Pool Period, Adverse Events by SOC and Sex, Percent of Patients



Examination of racial differences in frequency of events by SOC reveals little difference between “Asians” and “white”. The “BLACK OR AFRICAN AMERICAN” racial group has more divergences from “Asians” and “white” but the group n is small which may distort the proportionate representation of individual preferred terms in each SOC compared to groups with an sample size that is 8 times greater, [Figure 83](#).

Figure 84 C021 Adverse Events by SOC and Sex, Percent of Patients



Distribution of the proportion of adverse events by SOC across racial groups was examined, Figure 85. There were 8 SOC with differences between groups $\geq 7\%$, These may be seen in Figure 86. The most notable differences were seen in “Nervous System Disorders” and “General disorders and administration site conditions” with a maximum difference in number of patients of 38% and

30% respectively. In the “Nervous System disorders” SOC the racial group “BLACK OR AFRICAN AMERICAN” was seen to have a frequency of these events of 74% while “AMERICAN INDIAN OR ALASKA NATIVE” had a frequency of 44%.

Figure 85 C021, Adverse Events by SOC and Race, Percent of Patients, (Native Hawaiian / Pacific Islander Excluded due to small n=5)

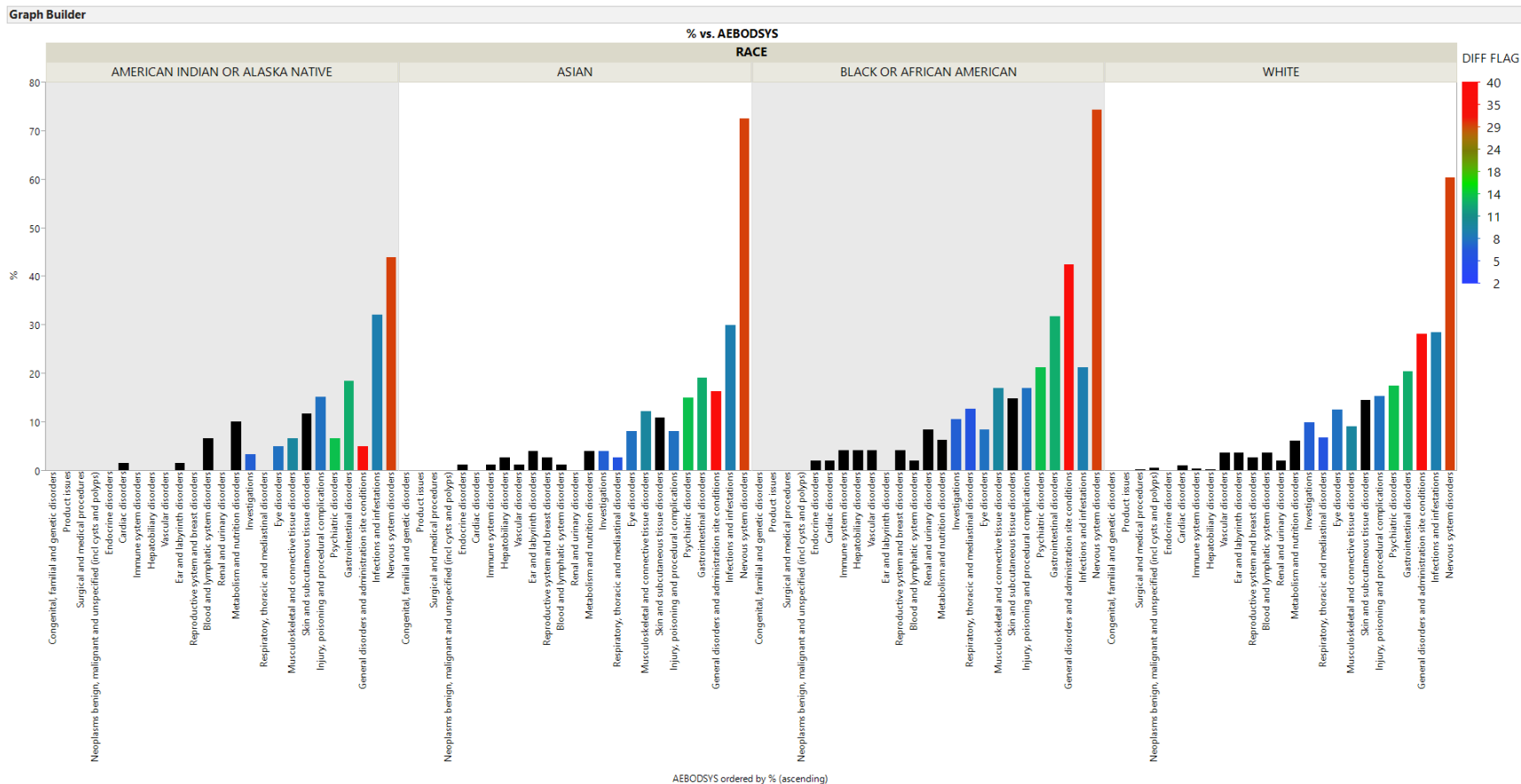
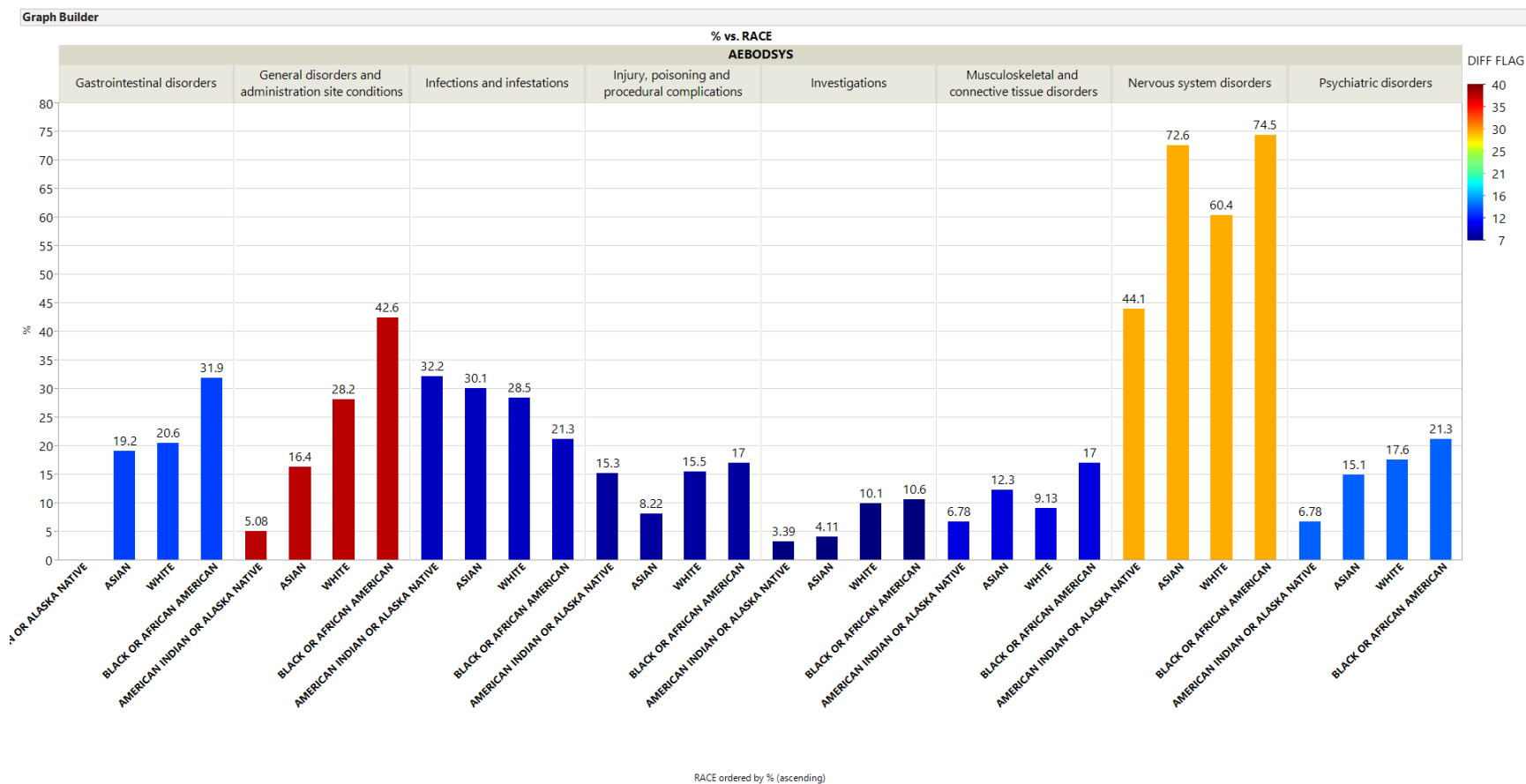


Figure 86 C021, Adverse Events by SOC and Race, Percent of Patients, SOC with Racial Differences $\geq 7\%$ (Native Hawaiian / Pacific Islander Excluded due to small n=5)



Reviewer Comment, Demographic Differences

In the C013-c017 pool there is little difference in proportions of events among the SOCs by sex, with the exception of “gastrointestinal disorders where there is an excess proportion in females over males of 10.1%. Racial differences in this pool were small between “Asians” and “White”. There were irregular differences between these two groups and “BLACK OR AFRICAN AMERICAN” that is due to the small sample size in the latter group.

8.8. Specific Safety Studies/Clinical Trials

C021

Study C021 was undertaken to evaluate the safety and pharmacokinetics (PK) of YKP3089 and concomitant antiepileptic drugs (AEDs) when administered as adjunctive therapy for the treatment of partial seizures. An additional purpose was to assess the risk of DRESS syndrome when cenobamate treatment is initiated at a reduced dose escalation relative to the phase 1 and pivotal studies. As noted in the discussion of DRESS risk in Section 2868.6.1 [DRESS Risk](#) there was a positive relationship seen in the development program between titration rate and hypersensitivity reactions.

The IND was placed on partial clinical hold due the occurrence of a two probable cases of DRESS and a case with a fatal outcome in the TQT study C020 on November 25, 2015. The partial clinical hold allowed continued treatment of patients on cenobamate treatment for ≥ 4 months, required that healthy volunteer subjects be tapered and discontinued with no new patients allow to enter into cenobamate treatment. In addition, there was requirement to explore the DRESS safety signal and identify measures to ensure patient safety.

In response to the partial clinical hold the sponsor proposed measures to prevent new cases of DRESS, to achieve early detection and evaluation of potential DRESS cases and ensure there is rapid reaction and treatment for any patient identified with DRESS.

A planned safety study C021 was underway at the time of the imposed partial clinical hold. In the “Partial Clinical Hold Complete Response” of 1/25/16 the sponsor proposed measures to satisfy the deficiencies identified in the “Partial Clinical Hold” of 11/25/15. These measures included the following items:

- Exclusion of patients with a history of any drug induced rash or hypersensitivity reaction
- Exclusion of patients with a history of a first degree relative that has had a serious cutaneous adverse reaction
- Reduce the rate of cenobamate dose escalation during titration
- Education of investigators to achieve a high level of awareness and capability ot recognize DRESS
- Dispense a laminated card for study patients to carry that contains DRESS warning

information and instructions on obtaining appropriate treatment in the event a symptom is identified.

- A skin assessment diary
- Identification of local specialists that have expertise in DRESS proximate to each study site
- Measures to evaluate suspected DRESS cases to facilitate diagnosis in a timely manner. These measures included-
 - Skin/Hypersensitivity assessment
 - Physical examination/rash assessment
 - Referral to local expert
 - Notification of the safety advisory board
- Measures to institute care of patients who develop DRESS
 - Drug withdrawal
 - Medical specialist care
 - Administration of steroids

The above measures were integrated into study C021 when the “Continue Partial Clinical Hold” letter allowing new patients or subjects to enter study with cenobamate treatment up to a dose of 200mg/day. This response was issued on 2/26/16 in response to the sponsor’s submission of 1/25/19.

During early 2017 discussion with our statistical team concluded that a study with a prespecified endpoint of 0 new cases of DRESS at the new modified reduced cenobamate dose escalation with a sample size of 1000 would be acceptable to limit the upper 95% CI to 0.3% DRESS frequency. The Division did have a concern that if any DRESS cases emerged in the study that it would fail to inform the question of upper boundary of DRESS frequency. Subsequently, as of April 23, 2018, a total of 1339 subjects received YKP3089 and were analyzed. The total includes 1110 subjects exposed for at least 6 months.

Study C021 Core Outline

Objective: The objective is to evaluate the safety and pharmacokinetics of YKP3089 and concomitant AEDs when administered as adjunctive therapy for the treatment of partial seizures. The evaluations will include:

1. Phenytoin-YKP3089 interaction
2. Phenobarbital-YKP3089 interaction
3. Long term safety of YKP3089 as adjunctive therapy in subjects with partial onset seizures
4. Population pharmacokinetics of YKP3089 and concomitant AEDs

Methodology:

This was a multicenter, open-label study in subjects with poorly controlled partial seizures consisted of a screening period, an open-label titration phase, an open-label maintenance phase, and for subjects discontinuing, a taper period and a follow-up visit.

The titration phase included 7 study visits (Visit 2 to Visit 8) and the maintenance phase included up to 6 visits in the first year (Visit 9 to Visit 14). During the first 16 weeks of treatment with YKP3089, visits occurred every 2 weeks. The follow-up visit (Visit 15) was to occur 14 days after last dose. Subjects who benefited from treatment may have continued beyond Year 1 with visits occurring every 3 months.

Design

This was a multicenter, open label study in subjects with poorly controlled partial seizures. Study structure included a screening period, OL irritation phase and OL maintenance phase with a taper and follow up. Patient concomitant medication subgroups will include at least 20 subjects taking phenytoin and at least 20 subjects taking phenobarbital with a group taking AEDs other than phenytoin or phenobarbital.

Screening Period: up to 21 days- assessment for study eligibility

Titration Phase:

The titration period on stable doses of other concomitant AEDs will be 12 weeks. Increasing doses of YKP3089 will be administered (50, 100, 150 and 200mg/day) at 2-week intervals, see [Table 100](#). If signs or symptoms of phenytoin or phenobarbital dose related toxicity are found at a regularly scheduled visit an additional phenobarbital or phenytoin plasma level should be obtained from a local laboratory. The dosage of phenytoin or phenobarbital can be reduced by 25-33% at the discretion of the principal investigator at that visit or when the level is available. Further reduction of phenytoin or phenobarbital during the titration phase will be allowed based on the investigator's clinical judgment of balance between adverse events and efficacy. A maximum reduction of ~2/3 of the total baseline dose of phenytoin or phenobarbital will be allowed. Prior to initiating YKP3089, subjects at US sites only will have trough concomitant AED levels (oxcarbazepine, topiramate, lamotrigine, lacosamide, clobazam, perampanel and levetiracetam only) drawn at Visit 2. Patients taking AEDs other than PHT or PB may have adjustments of cenobamate dose during the titration phase. If clinically indicated titration can be stopped below 200mg cenobamate / day but a minimum of 50mg/day is required to continue in the study.

Table 100 C021 Cenobamate Titration Schedule

Cenobamate mg/day					
Week 1 & 2	Week 3 & 4	Week 5 & 6	Week 7 & 8	Week 9 & 10	Week 11 & 12
12.5	25	50	100	150	200

During the maintenance phase the investigator may add (except phenytoin or phenobarbital), remove, or adjust (including phenytoin or phenobarbital) the dosage of any concomitant AEDs, as clinically indicated, [Table 101](#). Monotherapy with YKP3089 will not be allowed. In the event of poor tolerability, the investigator may instruct the subject to take the dose of study medication in the evening or divide the total daily dose into 2 doses. Subjects will follow the schedule of study visits and assessments detailed in [Table 102](#). After 12 months of participation in the open-label treatment period, subjects will be re-evaluated. Those who are benefiting from treatment with YKP3089 may continue use of the drug at the discretion of the investigator.

For patients in the cohort taking other concomitant AEDs, the initial target dose will be 200 mg/day. If the investigator feels that a subject requires a dose that is higher than 200 mg/day, the dose can be increased to a maximum of 400 mg/day once the target dose of 200 mg/day was reached. The upward dose adjustments should occur every other week in increments of 50-mg/day. If the investigator feels that a subject requires a dose that is lower than 200 mg/day, the dose can be reduced to a minimum of 50 mg/day once the target dose of 200 mg/day was reached. The downward dose adjustments may occur weekly by 100-mg/day or 50-mg/day. However, the downward rate of change may be more rapid or slow as clinically indicated.

Table 101 Study C021 Dose Adjustment Rules

Cohort	Subjects taking Phenytoin or Phenobarbital	Subjects taking AEDs other than Phenytoin or Phenobarbital
Adjustments of any Concomitant AEDs	Allowed	Allowed
Adjustments of YKP3089	Allowed	Allowed
Adjustment of Phenytoin or Phenobarbital	Allowed	Not Applicable

Inclusion:

- Male or Female ≥ 18 years of age with an upper age limit of 70 years
- Weight at least 40kg
- Diagnosis of epilepsy according to the ILEAE Classification- established by clinical history and EEG
- Uncontrolled partial seizures and require additional AED therapy despite treatment with at least one AED within approximately the last 2 years
- Currently on stable AED treatment- receiving stable dose of 1 to 3 AEDs for at least 3 weeks prior to Visit 2
- Benzodiazepines at least once per week during the 1 month prior to Visit 1 for epilepsy or anxiety will be counted as 1 AED and must be continued unchanged throughout the study.

- Computed tomography or MRI scan performed within the past 10 years that excluded a progressive cause of epilepsy

Exclusion:

- History of a serious drug induced hypersensitivity reaction.
- History of a 1st degree relative with a serious cutaneous drug-induced adverse reaction
- History of serious systemic disease
- Subjects taking phenytoin must not be taking phenobarbital or primidone; subjects taking phenobarbital must not be taking phenytoin or primidone
- Subjects taking concomitant AEDs other than phenytoin or phenobarbital, must not be taking phenytoin or phenobarbital or primidone
- Subjects with clinical evidence of phenytoin or phenobarbital toxicity
- A history of nonepileptic or psychogenic seizures
- Presence of only nonmotor simple partial seizures or primary generalized epilepsies
- Any clinically significant laboratory abnormality that in the opinion of the investigator would exclude the subject from the study
- Evidence of significant active hepatic disease
- Active CNS infection, demyelinating disease, degenerative neurologic disease or any CNS disease deemed to be progressive.
- Any clinically significant psychiatric illness
- Presence of psychotic disorders or unstable recurrent affective disorders
- History of alcoholism, drug abuse or addiction
- Current use of felbamate with less than 18 months of continuous exposure
- Current or recent use of vigabatrin or ezogabine.
- History of status epilepticus within 3 months of Visit 1
- Screening laboratory test demonstrates abnormal renal function
- ABS neutrophil count less than 1500/ul.
- Clinical or ECG evidence of serious cardiac disease. uncontrolled heart failure, major arrhythmias or QTcF less than 340ms or > 450ms and >470 in females.
- Platelet counts lower than 80000/uL in subject treated with VPA
- A yes answer to Question 1 or 2 of the C-SSRS Ideation Section in the past 6 months or a yes answer to any of the Suicidal Behavior Questions in the past 2 years.
- More than 1 lifetime suicide attempt
- Current use of any of the following medications: clopidogrel, fluvoxamine, amitriptyline, clomipramine, bupropion, methadone, ifosfamide, cyclophosphamide, efavirenz, fosphenytoin, ethotoin, or mephenytoin.
- Presence of congenital short QT syndrome

Study Endpoints

PK:

Sparse PK blood samples will be collected to evaluate YKP3089 and relevant concomitant AED

exposure using a population pharmacokinetics approach. This will allow for the investigation of potential effects of covariates on the pharmacokinetics of YKP3089 or other concomitant AEDs. YKP3089 and other concomitant plasma concentration data collected from this study will be pooled with relevant data from other YKP3089 clinical studies for population PK analysis

Safety:

Safety will be assessed by the nature, frequency, and severity of treatment-emergent spontaneously reported AEs, dropouts due to AEs, overall dropout rates, and changes from baseline in vital signs, physical exams, clinical laboratory evaluations, C-SSRS and 12-lead ECGs, in YKP3089-treated subjects.

Table 102 Study C021 Schedule of Assessments

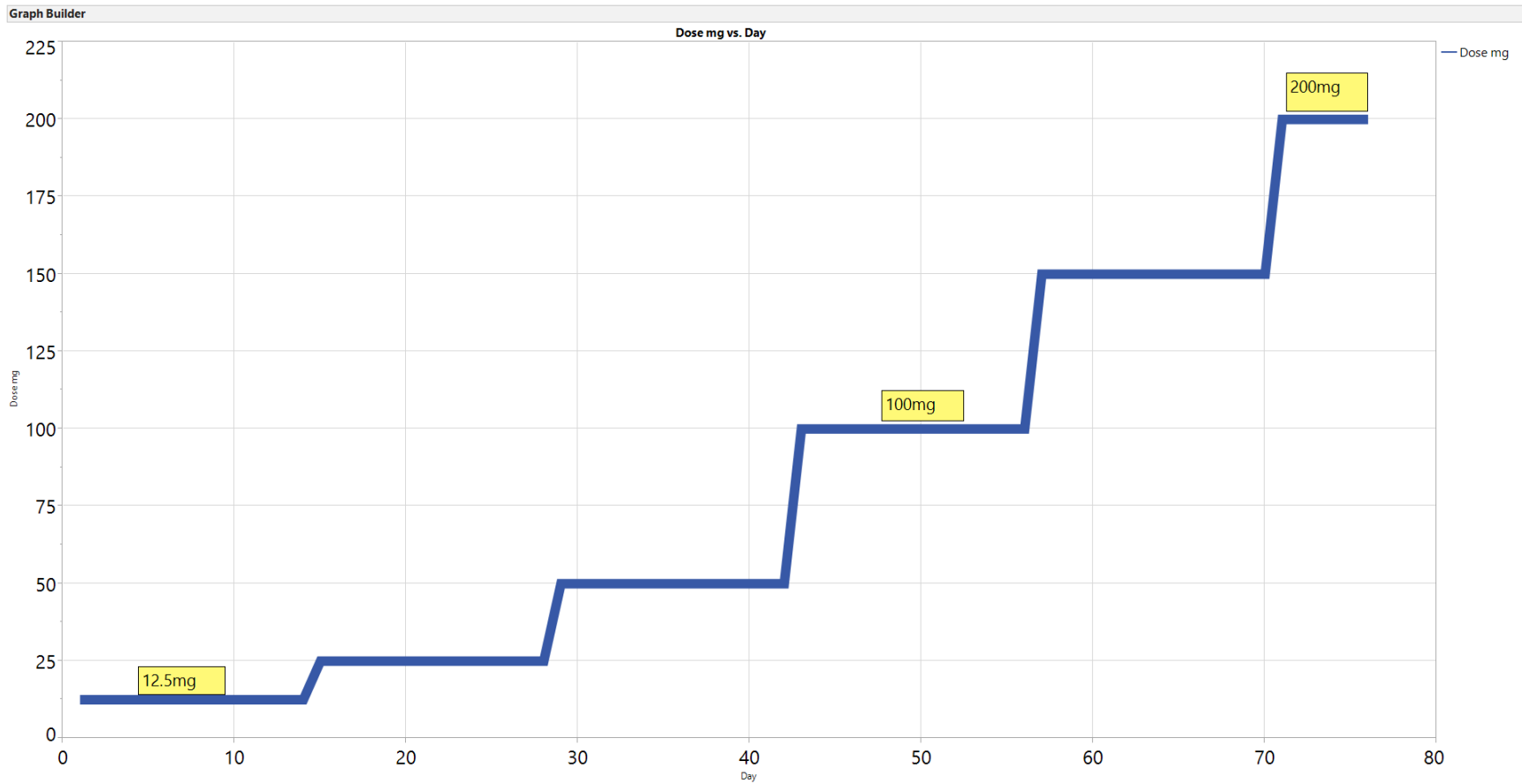
C021	Screening	Treatment Period														End of Study Follow-up
		Titration Phase							Maintenance Phase							
	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	Day -21	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 143	Day 203	Day 263	Day 365	Every 3 months ^a	14 days after the last dose
Informed Consent	X															
Inclusion/exclusion	X	X														
Demographics, medical and seizure history	X															
Vital signs ^b	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height ^c and Weight	X			X								X		X	X ^l	X
Full physical exam	X		X ^p	X ^p	X ^p	X ^p	X ^p	X ^p	X ^p	X ^p				X	X ^m	
Full neurologic exam	X													X		X
Brief neurologic exam ^d		X	X	X	X	X	X	X	X	X	X	X	X		X	
C-SSRS ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG ^f	X													X	X ^m	
Serum pregnancy test ^g	X															X

C021	Screening	Treatment Period														End of Study Follow-up
		Titration Phase							Maintenance Phase							
	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	Day -21	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 143	Day 203	Day 263	Day 365	Every 3 months ^a	14 days after the last dose
Urine pregnancy test ^g		X			X				X		X	X	X	X	X ^r	
Clinical Laboratory safety assessment ^h	X		X	X	X	X	X	X	X	X		X	X	X	X ^l	X
Urinalysis	X													X	X ^m	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
YKP3089 PK Draw ⁱ								X	X							
Phenytoin or phenobarbital PK draw ^j		X ⁿ		X	X	X	X	X								
Concomitant AED PK Draw ^k		X ⁿ						X	X							

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 Steven Dinsmore, DO
 NDA 212839 (cenobamate) XCOPRI

C021	Screening	Treatment Period														End of Study Follow-up
		Titration Phase							Maintenance Phase							
Assessment	Visit 1 Safety baseline	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14 or Termination Visit	After 1 year of treatment	Visit 15
Assessment	Day -21	Day 1	Day 15	Day 29	Day 43	Day 57	Day 71	Day 85	Day 99	Day 113	Day 143	Day 203	Day 263	Day 365	Every 3 months ^a	14 days after the last dose
EEG and MRI or CT scan ^o	X															
Follow up calls		X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q	X ^q							
Dispense Laminated Safety Card		X	X	X	X	X	X	X	X							

Figure 87 C021 Cenobamate Dose Titration Schedule (200mg at Day 71)



Study Results

As of April 23, 2018, a total of 1339 subjects received YKP3089 and were analyzed. The total includes 1110 subjects exposed for at least 6 months.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

8.9.2. Human Reproduction and Pregnancy

Female subjects who were pregnant or lactating were excluded from enrolling in the cenobamate clinical studies. However, 10 cenobamate-treated subjects had pregnancies reported across the clinical development program. [Table 103](#) lists each subject by study, the action taken with study drug, and the pregnancy outcome.

Table 103 Pregnancy Outcomes for Patients or Subjects Who Were Pregnant on Cenobamate

Subject ID	Study Number	Action Taken with Study Drug	Pregnancy Outcome
(b) (6)	YKP3089C013 (OLE)	Drug withdrawn	Ectopic Pregnancy (SAE)
	YKP3089C013 (OLE)	Drug withdrawn	Live Birth (normal)
	YKP3089C017 (OLE)	Study drug continued	Live Birth (normal)
	YKP3089C017 (OLE)	Drug withdrawn	Elective termination
	YKP3089C021	Drug withdrawn	Elective termination
	YKP3089C021	Study drug continued	EDD: 21-Sep-2018
	YKP3089C021	Drug withdrawn	EDD: unknown
	YKP3089C021	Study drug continued	Elective termination
	YKP3089C021	Study drug continued	Abortion spontaneous
	YKP3089C029	Completed study	Abortion spontaneous

8.9.3. Pediatrics and Assessment of Effects on Growth

N/A Pediatric populations will be addressed in post marketing by PREA requirements

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no intentional overdoses of cenobamate.

Potential withdrawal effects were explored in the phase 1 studies, unconfounded by concomitant antiepilepsy drugs, see [8.5 Phase 1 Safety](#). The temporal relationship and the implied medial physiology of several preferred terms identified during the end of treatment interval are consistent with a cenobamate withdrawal effect. The terms most likely to have a causal relationship are “insomnia”, “anxiety”, “depressed mood”, “nightmare”, “decreased appetite”, “tremor”, “body temperature increased”, “chills”, “heart rate increased”, “nervousness”, “nightmare”, and “tachycardia”.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

No Postmarketing experience is available

8.10.2. Expectations on Safety in the Postmarket Setting

8.10.3. Additional Safety Issues From Other Disciplines

8.11. Integrated Assessment of Safety

Exposure; see Section [8.2.1, Overall Exposure](#)

Examination of safety dataset demographics reveals the set is well balance by sex. Race and ethnicity representation is in alignment with the US population for “WHITE” and “HISPANIC OR LATINO” but the “BLACK OR AFRICAN AMERICAN” subset is under represented.

The clinical studies were adequate in frequency of safety assessments and capture of safety metrics including physical examination, vital signs, ECG, laboratory investigations including hematology and clinical chemistry. Potential confounding variables of past medical history and concomitant medications were also recorded. Required clinical case narratives were provided as well as case report forms.

A primary safety concern present at the outset of this NDA review was DRESS risk. DRESS emerged during development just after the end of phase 2 meeting (EOP2). Within a month a fatality of a healthy volunteer was identified in the thorough QT study, due to eosinophilic myocarditis that developed during DRSS syndrome. A partial clinical hold was placed on 11/25/15 for new subject enrolment and subjects that had been treated for less than 4 months. On 2/26/16 partial hold was continued with the condition that new subject enrollment could resume but maximum cenobamate dose could not exceed 200mg. On 6/18/16 partial clinical hold was continued with allowance that a maximum dose of 400mg was allowed. During this interval study C021 that had been initiated on 11/9/15 was modified under discussion with the Division, to assess strategies to reduce DRESS risk and assure an acceptable risk boundary. An agreement was reached that a sample size of 1200 patient with exposure for at least 6 months

would be adequate to cap the DRESS risk at 0.3% if the upper bound 95% confidence interval of DRESS frequency during the study was demonstrated to be 0.3%. This condition could only be met if no DRESS cases emerged in study C021 (point estimate 0, with upper bound 95% CI = 0.3%).

A core strategy to reduce DRESS risk in study C021 was a reduced titration schedule compared to the phase 1 and pivotal studies. The initial dose begins at 12.5mg and does not escalate for 2 weeks. After 2 weeks the dose is escalated to 25mg for an additional 2 weeks. To view the complete, modified, reduced schedule see Section 8.6.1 [DRESS Risk](#). In addition, patients were informed of the risk and given a laminated card that was to be carried. This card contained information on potential DRESS features as well as instructions when to go to an emergency room. Subsequently, in study C021 there were 1339 patients enrolled where 804 were treated for 6 months or longer and 306 were treated for 1 year or longer. There were no further DRESS cases identified. Due to the increased pharmacovigilance patients that developed rash or other features of suspicion were withdrawn from the study resulting in 66 withdrawals.

Examination of the safety dataset did reveal hypersensitivity events could occur early and with substantial severity. This was seen where 4 patients / subjects developed substantive hypersensitive features on day 1 or day 2 of cenobamate dosing, see [Rapid Onset Hypersensitivity Events](#).

Examination of the distribution of adverse event SOCs by demographic subsets revealed a higher frequency of events in the “neurologic disorders” in females compared to males. There was also an excess of events in the SOC “General disorders and administration site conditions” and “Gastrointestinal disorders” in the “BLACK OR AFRICAN AMERICAN” subgroup compared to “WHITES” and “ASIANS”. However, the “BLACK OR AFRICAN AMERICAN” population is small and may not provide an accurate representation of adverse events compared to larger populations.

QT shortening was identified in the safety evaluation of cenobamate. Formal cardiac ECG studies demonstrated shortening of the QT interval (mean = 16 msec, for doses >400 mg daily) with cenobamate. In a placebo-controlled study of the QT interval (study number YKP3089C020), a higher percentage of cenobamate-treated subjects (31% at 200 mg and 66% at 500 mg) had a QT shortening of greater than 20 ms compared to placebo (6-17%). Reductions of the QTc interval below 300 ms were not observed. The magnitude of the QTc shortening is similar to that associated with rufinamide. Similar language for labeling will be used.

Adverse events in the SOC “nervous system disorders” were the most frequent in the safety dataset and are dose-related and very notably separate from placebo at the 400mg dose, [Figure 42](#). Examination of the ISS reveals the most common preferred terms within this SOC are “dizziness”, “somnolence”, and “balance disorder” (headache in 3rd place is discussed separately). In the overall phase 2-3 dataset 1.9% of patient had discontinuation of cenobamate

for those three preferred term adverse events. There were 12 patients with these same adverse events, “dizziness”, “somnolence”, and “balance disorder”, that were entered as an SAE, although none of these was withdrawn. Expressed as a proportion of patients that experience the top three “nervous system disorder” events, those who were discontinued represent 4.8% and those with SAEs represent 1.5%. This analysis reveals that a low frequency, <5%, of these common adverse events interfered with the course of cenobamate treatment.

Additional issues that emerged on broader review of the cenobamate safety data are QT shortening, appendicitis, hyponatremia, hyperkalemia, headache, constipation, psychiatric events, cardiac adverse events, hepatic transaminase adverse events, and hypophosphatemia. As review progressed and potential issues were identified, they were added to Section 8.4.5, [Significant Adverse Events](#) for final adjudication.

As the totality of the NDA safety information was integrated appendicitis does have a frequency that is higher than the background rate. There was no correlation identified with other potentially coexisting or synergistic physiology such as frequency of overall infections, leukocytes or neutrophils. There was an association with a decline in globulin in a few cases, but no clear informative correlations emerged.

There was a clear post-baseline high frequency of hyponatremia seen in clinical studies. However, further exploration revealed that all instances were confounded by concomitant treatment with oxcarbazepine or carbamazepine. There was separation between placebo and cenobamate treatment arms in the controlled study data. However, the confounding by medications with a high frequency of hyponatremia causes difficulty in determine the magnitude of separation from placebo that is sufficient to allow a conclusion that an independent effect of cenobamate is present.

There were few adverse event entries for the term “hyperkalemia” but as assessment of the clinical laboratory data proceeded, an excess of post baseline OORR high potassium values was identified. The frequency of these events is sufficient to add an entry for “hyperkalemia” or increased potassium to section 6 of labeling.

Headache is a notable adverse effect of cenobamate due to the frequency of this event rather than the severity or medical threat. There were 460 instances from 280 (14.4%) patients where only one was entered as an SAE. From among the 460 instances 72% were identified as “mild” by the investigator, 26% as “moderate and 2.4% as severe. The frequency of headache is of similar magnitude to central nervous system adverse effects seen in cenobamate treatment.

Constipation emerged in review as an event of interest due to the high frequency. The co-investigation of “Gastrointestinal disorders” with “constipation” did not reveal any unifying process or family of related adverse events. Constipation was common and there was a single SAE of “obstipation” which was likely related to constipation because it was relieved by an enema. Proposed labeling covers this event in section 6, adverse reaction table.

Psychiatric disorders reached a threshold of increased concern in review due to the identification of several adverse events of “psychotic disorder” identified in the review of adverse events. These events are high impact, disruptive events for patient, family and / or caregiver. There were also two completed suicides and one particularly violent suicide attempt through self-inflicted stab wounds. There is a potential signal for an association of cenobamate with “psychiatric disorder” preferred terms, discussed in Section 8.4.5 [Psychiatric](#). The totality of the safety review reveals that due to the severity of background illness (refractory epilepsy, post ictal phenomena) and potentially confounding concomitant medications, the frequency of the psychiatric adverse events do not reach a substantive threshold for additional labeling.

Cardiac adverse events emerged as an area of focus due to the identification in “deaths” of fatal outcome events of “cardiac arrest”, “cardiogenic shock” and “myocardial infarction”. One patient had a background cardiac risk history, a second may have been SUDEP. The third case with the shortest latency from cenobamate start of 1.9 years had no clear cause. In addition, a bifascicular block and a complete AV block were seen in the dataset. There were also 10 patients with a syncopal event. The patient with bifascicular block was found to be on placebo. The patient with complete heart block did not have a strong temporal relation to cenobamate initiation, it began on day 185 and it was confounded by concomitant treatment with lacosamide. Examination of syncope revealed sporadic events across an exposure period from day 9 to 542 involving 0.6% of patients. None of the syncope were entered as an SAE and none had cenobamate discontinued. Overall, the analysis of events did not identify a trend of threatening cardiac events with compelling temporal relationship or a sufficiently high frequency to conclude there is a cenobamate specific cardiac safety signal.

Hepatic transaminases: Review of the adverse events and laboratory dataset did not reveal a high frequency or severity of ALT elevation. There was a dose related increase of OORR high values in study C017, several of these events were > 3 x ULN, also with a dose related frequency. There were 32 (1.7%) patients with 42 instances of ALT > 3 x ULN in the safety dataset but there was a single outlier with an elevation to 7.6 x ULN with no increase in bilirubin. There were no Hy’s law cases. Overall, there was no severe trend detected for sequential, sustained and frequent highly increased values of ALT or AST. There was a modest signal, however, based on the dose related laboratory event in study C017 and an occurrence of > 3 x ULN in 1.7% of cenobamate treatment in the ISS.

Due to 3 patient with and adverse entry of “visual impairment” there was exploration of the safety database for a visual dysfunction signal. Most instances were associated with central nervous system event that may result in a non-specific experience of visual disturbance. Overall, examination of terms potentially related to visual acuity dysfunction did not reveal a signal for a cenobamate associated effect on visual acuity.

Evaluation for seizure worsening related to cenobamate treatment there was no evidence of a pattern consistent with a seizure worsening effect.

Integrated Assessment, Summary:

The primary safety concern identified with cenobamate treatment is the risk of DRESS syndrome. The potential risk is mitigated with slow dose escalation during titration. The zero frequency of DRESS, sample size, and duration of exposure offer assurance that DRESS risk is in a range similar to the occurrence of serious skin reactions seen with lamotrigine treatment, a prominent AED in the therapeutic armamentarium. Cenobamate does demonstrate a high propensity toward hypersensitive response; this is seen in the safety dataset, where there were cases of rapid onset of features after a few doses. It is uncertain if these and other hypersensitivity reactions that resulted in patient withdrawal from study C021 forecast DRESS syndrome.

QTc shortening was identified and evaluated by a TQT study. The adverse event profile did not reveal a signal for potentially related events. This will be entered into labeling in Section 5.

An uncommon adverse event of “appendicitis” was observed. There is no strong temporal relationship for these events but there is a notable increase in frequency over the expected background rate. A signal for adverse neuropsychiatric events may be present, but the totality of evidence for attribution to cenobamate is inconclusive, and the most severe of these adverse reactions, suicide and suicidality is present as a class warning for AEDs. Also identified in the safety review were hyperkalemia and hyponatremia. There was a modest signal for increase ALT seen in a dose related ALT increase in controlled study data, 32 (1.7%) patients with 42 instances of ALT > 3 x ULN in Phase 2-3 study exposure, and a single serious outlier of increased ALT without an alternative explanation. Among common adverse events, there were features of CNS dysfunction including dizziness, somnolence and balance disorder often seen in AED treatment.

Important negatives include the absence of a Hy’s law case. There was a trend of a decline in leukocytes and neutrophils, but when followed over time these tended to plateau and did not reach critical levels. There was no evidence of seizure worsening.

In section 5 there will be labeling additions of QTc Shortening. The reviewer is recommending an addition of hyperkalemia to a “Laboratory Abnormalities” subsection of Section 6. The trend of OORR high ALT seen in study C017 as well as the single severe outlier value are recommended for addition to the “Laboratory abnormalities” subsection. Addition of a “gastrointestinal disorders” heading in section 6 to contain “appendicitis” is also recommended, see Section [10.1, Prescription Drug Labeling](#).

9. Advisory Committee Meeting and Other External Consultations

None planned

10. Labeling Recommendations

10.1. Prescription Drug Labeling

10.1.1. QT Shortening

4 CONTRAINDICATIONS

Cenobamate is contraindicated in patients with Familial Short QT syndrome [see Warnings and Precautions (5.x)].

Section 5.x QT Shortening

Formal cardiac ECG studies demonstrated shortening of the QT interval (mean = 16 msec, for doses >400 mg daily) with cenobamate. In a placebo-controlled study of the QT interval, a higher percentage of TRADENAME-treated subjects (31% at 200 mg and 66% at 500 mg) had a QT shortening of greater than 20 ms compared to placebo (6-17%). Reductions of the QTc interval below 300 ms were not observed. The degree of QT shortening induced by cenobamate is without any known clinical risk. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Non-clinical data also indicate that QT shortening is associated with ventricular fibrillation. Patients with Familial Short QT syndrome should not be treated with cenobamate. Caution should be used when administering cenobamate with other drugs that shorten the QT interval [see Contraindications (4)].

10.1.2. Laboratory Abnormalities

Hepatic Transaminases

There was 1 (0.9%) patient in the 100mg treatment arm, 2 (1.8%) patients in the 200mg treatment arm, and 3 (2.7%) patients in the 400mg treatment arm and none in placebo, with a post baseline ALT elevation to > 3 x ULN. In the 400mg treatment arm the maximum ALT elevation was 7.6 X ULN.

Potassium

There was an excess of potassium values greater than 5meq/L (upper reference range) observed in pivotal studies. In study1 there were 8 (7%) patients in the placebo arm and 17 (17%) patients in the cenobamate arm with normal baseline values with at least one post baseline maximum value >5meq/L. In study 2 there was a dose related distribution where at

least one post baseline potassium value was >5meq/L in a dose related distribution, occurring in 5.6%, 8.3%, 9.1% and 10.8% of the placebo, 100mg, 200mg, and 400mg treatment arms respectively. Two patients had a maximum value of 5.9meq/L.

10.1.3. Other Adverse Reactions

The following is a list of adverse reactions reported by patients treated with cenobamate in controlled and open label clinical trials in adult patients with partial-onset seizures.

Gastrointestinal disorders:

There was an incidence of appendicitis in the overall clinical trial safety population of 2.9 cases of appendicitis / 1000 patient years of exposure that is in excess of the expected background rate in the general population.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS is planned. A patient medication guide will accompany labeling.

12. Postmarketing Requirements and Commitments

See approval letter for Postmarketing Requirements.

13. Appendices

13.1. References

See individual footnotes

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): C013, C017

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: <u>275</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant); N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant); N/A

13.1. Exposure Calculation

Total exposure is calculated using the ISS 120 day safety update ADEX.xpt dataset. Placebo only exposures are excluded. This leave 13,567 rows for 1946 Patients. A subset table is created for the 1945 entries for the variable EXDUR. The value for these entries is added to obtain 1138702 days. To exclude placebo exposure days in the double-blind interval of studies C013 and C017 all entries for the PARAMCD entry EXDUR1 where the entry for the variable TRT01A is “placebo” are identified. The value of all entries with these properties are added. This yields a value of 18138 days. This value is subtracted from the sum of all EXDUR values to yield 1120564 days. This value is divided by 365 to yield 3070 years of exposure across all 1945 phase 2 study patients.

13.2. Study C021 – Narrative Summaries

13.2.1. SAE Narrative Summaries

Study C021 SAE Key Case Narratives

YKP3089C021- (b) (6) Encephalitis

The patient experienced drowsiness, generalized weakness, headache and lumbago. On study day 119, the patient experienced the severe, life threatening, disabling, SAE of meningoencephalitis and was hospitalized. The family of the patient found the patient in bed, drowsy and with poor response to verbal stimuli or mobilization. The patient was taken to the emergency room. Her blood pressure was 128/84 mmHg, pulse 78, respiratory rate 19, somnolence, normal pupilar reflex, weakness in four extremities. Laboratory testing two days later revealed: creatinine 2.19 mg/dL, urea 72 mg/dL, BUN 32, DHL 1073, AST 322 U/L, ALT 167 U/L, GGT 145 U/L, total bilirubin 45 mg/dl, direct bilirubin 2.9 mg/dl, metabolic acidosis, pH 7.38 HCO₃ 11.2. Computed tomography of head was normal. The patient was treated with hydration and nasogastric tube. On 14 Dec-2017 the patient had stupor and clear data of meningeal irritation with Kernig and Brudzinski sign positive, thus puncture lumbar was performed the same day and cerebrospinal fluid (CSF) was reported with glucose level 10 mg/dl (serum glucose was unknown but apparently was normal) and protein level 600 mg/dl.

Five days after hospitalization, the patient had cardio respiratory arrest and required mechanical ventilation support and aminergic support, and a central line was placed. The patient was transferred to general surgery service. Another lumbar puncture was made on (b) (6) and CSF protein level was elevated, and glucose level was low. WBC was 2-3. CSF Ziehl-Neelsen stain, BAAR, Chinese ink staining gene expert and bacteriologic culture were negative on (b) (6). The patient had ventilator associated pneumonia and was treated with Imipenem (doses not provided). Aminergic and ventilator support were withdrawn on (b) (6) but there was no improvement in neurological state being found with minimally consciousness state. The study drug was withdrawn due to the event and the last dose was taken on (b) (6). The patient was discharged from the hospital and recovered with sequelae from the event of meningoencephalitis on (b) (6).

YKP3089C021- (b) (6) Herpes zoster

Subject (b) (6) a 56-year-old Caucasian female, was diagnosed with epilepsy in (b) (6). The subject was screened and signed informed consent on (b) (6), with current seizure types simple partial without motor and complex partial, for participation in “An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures.”

Relevant medical and surgical history included: left frontal corticectomy on (b) (6) insertion of seizure prediction device on (b) (6) and removal on (b) (6) depression ongoing since (b) (6) insomnia ongoing since (b) (6).

Concomitant medications included: escitalopram 40 mg oral once a day for depression, ongoing since (b) (6). Concomitant AED included: levetiracetam 1000 mg oral twice a day, ongoing since (b) (6) oxcarbazepine 1200 mg oral once a day, ongoing since (b) (6).

The first dose of YKP3089 12.5 mg was initiated on (b) (6). On (b) (6), the dose was increased to 25 mg which was further increased to 50 mg on (b) (6). The dose was up-titrated to 100 mg on (b) (6) further titrated to 150 mg on (b) (6). On (b) (6) the dose was increased to 200 mg. Since (b) (6) the subject was receiving 250 mg.

On (b) (6) (study day 296) the subject experienced the moderate serious adverse event of herpes zoster infection (ie. shingles) and was hospitalized on (b) (6). On (b) (6) subject experienced rash to left side of face which was diagnosed as herpes zoster. On (b) (6) subject was admitted from home to the hospital with VZV encephalitis and deranged liver function studies. Abdominal ultrasound showed cholelithiasis with a stone lodged in the gallbladder neck, no cholecystitis, mild hepatic steatosis. Chest x-ray showed moderately expanded lungs which appeared clear, no effusion, pneumothorax or pneumoperitoneum. CT brain showed no acute abnormality. The subject was treated with intravenous acyclovir 800 mg three times a day, oxycodone 2.5 mg oral as needed, nystatin 1 ml oral four times a day, pregabalin 25 mg oral twice a day, refresh liquid gel eye lubricant as needed, prochlorperazine maleate 5 mg oral three times a day. The study drug was not changed due to the event. On (b) (6) the subject recovered with sequelae from the event and was discharged home to continue intravenous acyclovir via PICC line.

YKP3089C021- (b) (6)

On an unknown day in (b) (6), (study day 102, estimated), the subject experienced the moderate SAE of psychosis with suspected delusions. The subject called the investigator on study day 193 and reported that he had been hospitalized since study day 191 due to the psychosis. According to the discharge summary, the family had noticed changes in the subject according to the police. He had frequently voiced the suspicion that he was being poisoned and that the family has evil intentions. He had offered to commit suicide for his family. He stated that he was not suicidal and only wanted to offer to commit suicide in order to ascertain the true intentions of the family. He wanted to live. All of this was caused by suspicious or overdue WhatsApp messages from family members. Subsequently, the family had notified the emergency medical services. The subject reported that he repeatedly felt for some time that he cannot rely on his family. He was afraid of being poisoned and had the feeling that a conspiracy was planned against him.

The subject had quit his job as an IT specialist in February. He stated that he had no problems with his work but complained about the overall environment being “too policial (sic).”

The subject reported that he had been taking a study medication since the fall but was uncertain about whether it helped to improve his condition. However, there was a conspicuous temporal correlation between the intake of the study medication, the development of the psychotic syndrome as well as the termination of employment. The efficacy of the study medication was inconclusive, an additional three questionable nocturnal seizures were reported to have occurred. In the right temporal epileptic zone, dialeptic as well as nocturnal generalized tonic-clonic and hypermotor/automotor seizures were reported, which occurred less than 1x per month.

The subject had a positive attitude toward the offer of inpatient. Acutely dangerous situations did not occur. He went back home to get his belongings and the antiepileptics and then returned to the hospital. The study medication was initially discontinued because of its questionable effect and its temporal correlation to the occurrence of the psychosis. In addition, we administered 2x 0.5 mg lorazepam. The medical history from his family included psychotic symptomatology associated with delusion of injury persisting for months. He believes there was a conspiracy against him and his mother is poisoning him. He had no aggressions, no suicide attempts and no suicidal threats. Psychopathological findings on admission: The subject was alert, fully conscious, fully oriented. He had mild concentration problems. Apprehension mildly impaired. Formal thinking mildly slowed down. Moderately systematized and highly dynamic delusion of reference and delusions of injury, no hallucinations. No depersonalization disorders. Euthymic mood. Drive was normal. Silent psychomotor function. He distances himself clearly from suicidality, no aggressive behavior against others. During the inpatient stay, successive worsening of the psychotic symptoms associated with delusions of persecution was observed, which by now seemed to dominate his actions. This was evidenced, for example, by the fact that members of the nursing staff were now part of his delusional experiences and he believed being poisoned by the medications of the hospital. Clearly disorganized and partially bizarre behavior. The study drug was discontinued due to the event of “psychosis” and the last dose was taken on study day 190.

On the morning of (b) (6) while no longer taking YKP3089 and still hospitalized, the subject experienced the severe SAE of suicide attempt. The subject was increasingly tense and irritated. At the doctor’s visit, he requested to be discharged immediately. After the urgent need to continue treatment was discussed with the subject, the subject was informed that a judicial hearing may otherwise be required to make a decision on this. The subject agreed to remain in the ward. Approximately 30 minutes later, the nursing staff was notified by another patient that the subject was found in his bed in a reclined position with a knife in his hand and bleeding severely. MRI performed on (b) (6) assessment: No indication of cerebral abnormalities. CT polytrauma on (b) (6): multiple stab wounds including right cervical without injury of the cervical vessels, one in the upper middle abdomen extending to the intraperitoneal cavity, two stab wounds in the liver without evidence of active bleeding, stab

injury in the right upper abdomen with herniation of fat tissue and small mesenteric vessels in the stab canal. Suspected injury of the inferior epigastric artery without indication of active bleeding. 26 mm size, arterial hypervascular hepatic lesion in segment VI, adenoma suspected. Complementary Primovist assisted MRI recommended.

The subject received emergency care and was transferred via the shock room to the emergency surgery department. The physical examination revealed approx. 10 abdominal stab wounds, 3 stab wounds on the right side of the neck, a 20cm long slash wound on the left forearm and a 5cm long slash wound on the right forearm. The CT procedure revealed liver injury as well as injury of an abdominal vessel, which is why the colleagues in General Surgery performed exploratory laparoscopy with subsequent drainage placement. Following surgical treatment, the intubated patient was transferred to the anesthesia intensive care unit. Psychiatric assessment was again performed after extubation. When the subject was asked about the events in the morning, he stated not remembering anything. He denied injuring himself with suicidal intentions. During the discussion, subject displayed parathymic laughter multiple times, he appeared distrustful and demanded the immediate termination of the discussion and indicated he will now talk only to a lawyer. The patient also did not agree to the continuation of intensive care treatment. Because of the remaining threat of self-aggression and the possibility of aggression against others, protective restraints were discussed with the colleagues from anesthesia. As a result of the restraint, the subject was extremely tense and pulled his CVC. The officers of the municipal standards office issued a warrant to take him into police custody. The subject was subsequently housed as per judicial decision at the PsychKG until (b) (6) because the subject was not able to control himself due to the psychotic symptoms associated with the misjudgment of people and situations as well as the most likely delusionally motivated suicide attempt.

The subject was subsequently transferred to our protected hospital and continued to be distrustful and in transparent when communicating with him. On anxiolytic therapy with diazepam, the subject's psychomotor activity decreased significantly. We initiated an antipsychotic medication therapy consisting of amisulpride and later switched the medication to Haldol 3mg/d. On these drugs, the subject was increasingly more approachable and less distrustful. After the expiration of the judicial decision, [redacted] agreed to continue voluntary inpatient treatment. Close contact to the family of the patient showed as well that the patient had achieved the "previous state." In direct contact, the patient continued to demonstrate prolonged response latency. The subject was discharged from the hospital on study day 259 and recovered/resolved with sequelae from the events of psychosis with suspected delusions and suicide attempt.

Psychiatric Disorders

YKP3089C021- (b) (6) (PT-psychotic disorder): a 42 yo Caucasian female developed paranoid

delusions study day 11 at a cenobamate dose of 12.5mg daily. This continued despite treatment with aripiprazole. On study day 13 the cenobamate dose was increased to 25mg. On study day 18 the patient experienced worsened psychosis and was hospitalized. At admission the patient was physically and verbally aggressive, confrontational and paranoid. Paranoid ideation continued to worsen. Cenobamate was discontinued on study day 21. On study day 24 an EEG revealed bitemporal cortical irritability with rare left temporal sharp waves. No subclinical seizures were captured. The patient was discharged from the hospital on study day 37 after treatment with Zyprexa and the psychosis resolved over the subsequent 3 weeks. Causality assessment of psychotic episode: *There was a temporal relationship however, dechallenge is less certain due to initiation of antipsychotic therapy.*

YKP3089C021- (b) (6): (2 PT's "affective disorder & anxiety disorder) 57-year-old Caucasian female with a history of depression and postpartum depression. On study day 30 at a cenobamate dose of 50mg the patient complained of nightmares that were vivid terrifying dreams of her common law husband hurting her. This worsened over the next few days. She became depressed and weepy. She thought that her common law husband was stealing her money, raping her during seizures and physically abusing her (physical abuse of her by him had occurred in the past). On study day 50 the subject presented to the hospital and was admitted with the diagnosis of "unspecified bipolar 1 disorder, rule out mood disorder due to medical condition. Cenobamate was discontinued. The patient was discharged after 1 day. Treatment continued in the outpatient setting, On study day 58, 10 days after cenobamate was discontinued the patient was treated with risperidone and clonazepam. At last contact, study day 62, that was 14 days after study medication was discontinued the patient was reported "back to normal". *Causality Assessment: This delusional event had a temporal relationship and dechallenge response. Past history of underlying depression may indicate that cenobamate interacts with a background selective vulnerability.*

YKP3089C021- (b) (6) (PT-Major depression) 38 yo female, examined with a mental status change initially was evaluated in a psychiatric emergency room for a major depressive syndrome (study day 22) and was hospitalized. The patient denied suicidal ideation. Study drug was interrupted (at a dose of 25mg/day based on the ex.xpt file) for a day then resumed at 50mg/day. After this incremental increase in cenobamate the patient developed drowsiness and was again hospitalized on study day 31. On admission the patient was drowsy and had instability when walking. The neurologic exam revealed diplopia and ataxia. These events were noted to coincide with the addition of escitalopram. Escitalopram was stopped, lacosamide and levetiracetam was continued. The study drug was unchanged due to the event. The patient remained free of seizure and side effects and discharged from the hospital on study day 33. The patient subsequently continued cenobamate treatment in study C021 until day 540. *Causality Assessment: There is a temporal relationship to treatment, but the event was manageable indicated by continued treatment. The event is also confounded by concomitant lacosamide.*

YKP3089C021- (b) (6) (PT aggression): a 19 yo Caucasian male with a past medical history of

behavior disorder, epileptic personality disorder. The patient was on quetiapine 200 mg oral twice a day for interrupted suicide attempt. The patient had seizure exacerbation on study day 40 at cenobamate dose of 50mg. On study day 144 on a dose of 300mg cenobamate the patient became aggressive at a group home and threatened a female companion with a knife because she made him angry. The patient was admitted to the psychiatric unit for observation. After admission the patient missed 2 doses of cenobamate and had 2 grand mal seizures. Study drug was continued. Causality in this case is uncertain due to background history of psychiatric disorder and the potential CNS effect of breakthrough seizures. *Causality Assessment: There is no temporal relationship, confounded by pre-existing personality disorder.*

YKP3089C021- (b) (6) (PT- anxiety): 66 yo African American female with past history of encephalitis and generalized anxiety disorder. On study day 413 the patient experienced an anxiety attack and was hospitalized. The subject arrived by ambulance to the emergency department (ED), presented with chief complaint of a several hours long episode of intermittent weakness, shaking that alternated from right to the left side of her body, and slurred speech. In the ED, subject was speaking without slurring, and symptoms had improved. Blood pressure 124/76. heart rate 78, oxygen saturation 96%, a computerized tomogram (CT) of the brain showed mild atrophy consistent with patient age. The patient was discharged to home on the 3rd hospital day and cenobamate was continued until C021 study day 630. *Causality Assessment: No temporal relationship*

YKP3089C021- (b) (6) (PT Depression): 46 year old Caucasian female with a past history of depression. Concomitant medications included: duloxetine 180 mg oral once a day for anxiety, from (b) (6) to (b) (6), ziprasidone 40 mg oral once a day for psychosis, ongoing since (b) (6). The patient was hospitalized on study day 146 for a depressive episode that occurred in the context of the reemergence of seizures. During the admission, there were reported symptoms suggestive of PTSD including flashbacks, nightmares, constant hyperarousal and preoccupation with thoughts about past trauma. The subject had a history of engagement with the day program for similar depressive episodes and recently sought out a private psychiatrist in an outpatient setting. Prior to admission, the subject was seizure free for five weeks and when a subsequent seizure occurred, this resulted in lowering of her mood with significant themes of hopelessness, worthlessness and feeling burdensome on her family. Prior to admission, the subject wrote a suicide note to her family, with collateral information from the subject's spouse suggesting that the subject had been teary, low and distressed for many weeks prior. Duloxetine was increased to 210 mg and the event of depressive episode was considered resolved on study day 161. Cenobamate treatment was continued until day 364 of study C021. *Causality Assessment: There no temporal relationship, long latency to the event and confounded by background depression. The event was managed without drug withdrawal.*

YKP3089C021- (b) (6) (PT Postictal psychosis): a 39-year-old Caucasian female with a background history of depressive mood, ongoing since 2007. On study day 427 the subject experienced the moderate serious adverse event of postictal psychosis and was subsequently hospitalized. Prior to the psychosis event the patient experienced seizure breakthrough, on a

background of previously highly treatment resistant seizures. On study day 425 the patient had 2 complex partial seizures in a few hours. 2 days later the patient developed intermittent psychotic delusions and agitation. Per the discharge summary, the subject on admission was inaccurately oriented in place and time, in superficial, not always rational verbal contact. Emotionally labile, unadapted, with bouts of cheerfulness and irritation, periodically loud, energized, with increased drive. The subject made a few statements suggesting their delusional, mainly religious nature, reports the occurrence of cenesthetic hallucinations and thought broadcasting. The patient's psychotic and behavioral disorder resolved in part and the patient was discharged on the 6th day of hospitalization, study day 431. At outpatient follow up the next day the patient was report to be in stable good general and mental condition. The patient continued cenobamate treatment in study C021 until study day 545. The event may have been precipitated by seizure breakthrough. Continued treatment suggests this was an episodic breakthrough rather than sustained decline in efficacy. *Causality assessment: No temporal relationship. The event was managed without drug withdrawal. No confirmatory relationship to cenobamate.*

Gastrointestinal Disorders

YKP3089C021- (b) (6) (PT vomiting): a 19-year-old Caucasian male was diagnosed with a gastrointestinal virus with symptoms of vomiting and diarrhea on study day 126. The SAE of refractory vomiting was entered on study day 191 during recovery from another SAE of pneumonia entered on study day 161. The study drug was not changed due to the event. The patient recovered from the event of vomiting and was discharged from the hospital on study day 197. The patient continued treatment 400mg cenobamate in study C021 to day 711 (ex.xpt dataset). *Causal Assessment: There is a poor temporal relationship, treatment continued without drug withdrawal.*

YKP3089C021- (b) (6) (PT vomiting): a 58-year-old Caucasian female experienced the mild SAE of vomiting on study day 70 and was hospitalized from study day 77 to 78 while receiving 150mg of cenobamate daily. The caretaker noted that the subject had been unwell and was not tolerating oral fluid and meal, vomiting with lower abdominal pain (no diarrhea). Laboratory studied on day 78 revealed mild hypernatremia (148mmol/l) and blood creatinine elevated to 138umol/L (reference range not provided, textbook ULN 106 umol/L). C reactive protein was elevated at 18mg/L (reference range not provided, textbook ULN 10mg/L). On study day 116 the patient recovered from vomiting. On study day 105 the patient concurrently developed an SAE of urosepsis. On study day 160 the patient was discontinued from cenobamate treatment. Vomiting appears severe enough to cause mild hypernatremia. The elevated C reactive protein is nonspecific but may be due to underlying inflammatory process, cenobamate is suspect. Causality to both urosepsis and vomiting is uncertain because for the variable of background medical status. The patient requires a caregiver who also signs for medical care. *Causal assessment uncertain.*

YKP3089C021- (b) (6) (PT abdominal pain): 48-years-old Caucasian male problems appeared

to have begun around study day 379 at that time he had nausea and vomiting, approximately one month after escalation of cenobamate from 250mg to 300mg. the patient was feeling very weak and passed out on 2 occasions on study day 385 and the subject was brought to the hospital. At that time, they diagnosed him with dehydration, benign positional vertigo and syncope. The subject serum sodium on study day 385 was 128, as per the investigator the subject has occasionally mildly low sodium on his Aptiom which can give some SIAD-like syndrome. On study day 393, the subject experienced weakness, stomach bloating, and muscle aches and went to the Emergency Room (ER) and was admitted the same day. A Computerized tomogram (CT) of the abdomen and pelvis showed a markedly distended bladder, and normal appearing prostate. The subject was afebrile. Laboratory results included sodium which ranged from 125 to 129 (units and reference range not provided). While hospitalized, the subject was placed on a fluid restriction, and complained of less pain, and was voiding well. On study day 395, the subject was recovered from the events of Abdominal Pain (moderate severity) and Worsening Hyponatremia (mild severity) and was discharged the same day. *Causal Assessment: A causal relationship to cenobamate is uncertain. There is no temporal relationship but also no coherent medical analysis to explain the adverse event that appears more predominantly nausea and vomiting.*

YKP3089C021- (b) (6) (PT abdominal pain): a 29-year-old Caucasian female study day 438), the subject experienced the severe serious adverse event of abdominal pain, presented to the Emergency Department (ED) and was admitted. Beginning study day 190 the patient had an adverse event of gallstones that remained ongoing. On study day 439 the patient underwent an appendectomy and cholecystectomy. Discharge summary was unobtainable. The study drug was not changed. On study day 441 the patient was discharged. *Causal Assessment: There is no evidence for causal relationship to cenobamate. Causality is not supported by temporal relationship. Dechallenge cannot be assessed.*

YKP3089C021- (b) (6) (PT obstipation): a 44-year-old Caucasian male, experienced the moderate SAE of obstipation and was hospitalized on study day 18 while taking 25mg of cenobamate daily. The subject presented to the emergency medical service due to abdominal pain in epigastrium with propagation into the lumbar region on the left. The subject had no vomiting, no dysuria, no fever, and had a bowel movement that day. An ultrasound revealed an obstructed pancreas. During hospitalization the subject received analgesic and spasmolytic therapy, diet, and enema. During the enema he evacuated a large amount of stool. The study drug was not changed due to the event. On study day 20 the patient recovered from the event of obstipation. *Causal Assessment: Possibly causal relation to cenobamate, there is a positive temporal relationship and high frequency of "constipation" among clinical study adverse events.*

YKP3089C021- (b) (6) (PT enteritis): a 48-year-old African American female experienced the severe serious adverse event of abdominal pain, with nausea and vomiting and was admitted to the hospital on study day 687 on cenobamate 400mg. A CT scan of abdomen and pelvis with contrast demonstrated segmental small bowel wall thickening in the lower abdomen most compatible with Enteritis. There were distended loops of proximal to mid small bowel and

collapsed bowel distal to the thickened segment compatible with mechanical small bowel obstruction. There was no evidence of closed loop obstruction, volvulus, or internal hernia to account for thickening. Mild ascites which was likely reactive. Distended gallbladder without cholelithiasis or gallbladder wall thickening was identified. A repeat CT scan (date not reported) showed resolution of enteritis and small bowel obstruction (which was due to previous hysterectomy). She developed right lower lobe aspiration pneumonitis and was treated with antibiotics, with improvement. The subject underwent laparoscopic lysis of adhesions on (b) (6) - (b) (6) with uneventful recovery. Throughout the admission she continued to take study drug and other AEDs. The study drug was not changed due to the event. On study day 696, twelve days after onset, the subject recovered from the event of enteritis and was discharged. *Causal Assessment: There is no temporal relationship and an alternate etiology of enteritis and vomiting due to small bowel adhesions.*

YKP3089C021- (b) (6) (PT Lower gastrointestinal haemorrhage): 38-year-old Hispanic male experienced lower gastrointestinal bleeding and was hospitalized on study day 42. Laboratory results showed thrombocytopenia and elevated liver function tests likely secondary (*confounded*) to valproic acid. His VPA was 82. The subject also experienced the non-serious adverse event of eosinophilia. On study day 43 the abdominal pain and dizziness abated spontaneously. A colonoscopy was performed on (b) (6) and revealed mild diverticulosis involving the left side of the colon and external hemorrhoids (also reported as internal hemorrhoids). The external hemorrhoids were likely the source of the subject's bleeding. Cenobamate was discontinued on study day 42. *Causal Assessment: Cenobamate is not likely causal for internal hemorrhoids. Although eosinophilia is reported during the hospitalization there was no increase in eosinophils identified in the study directed laboratory values.*

YKP3089C021- (b) (6) (PT gastritis): a 58-year-old Caucasian female experienced (mild) gastritis and was hospitalized on study day 268 while receiving 150mg of cenobamate. The subject presented after a short- lasting episode of hematemesis after eating. Subsequently the subject also had one incident of tarry stools. The subject did not take any NSAIDs, nor anticoagulants. On admission BP was 150/80 mmHg, HR 63/min, RR 14/min, O2 sat 97%, abdomen soft, no guarding. On study day 269 an esophagogastroduodenoscopy was done which showed erythematous gastritis, H. Pylori test negative, no ulcers. No evidence of neoplasm, no active source of blood able to be determined. Z-line was normal, no Mallory-Weiss lesions, no hiatal hernia. The subject was admitted and was hemodynamically stable with unremarkable clotting parameters and a hemoglobin level of 12 g/dL. There was no further vomiting or passing of tarry stools. The study drug was not changed due to the event. On (b) (6) the subject recovered and was discharged. The exposure (ex.xpt dataset) identifies cenobamate treatment to study day 260. There is no clear cause of the local gastritis. *Causal relationship to cenobamate is possible due to absence of alternative etiology but the temporal relationship is not supportive.*

YKP3089C021- (b) (6) (PT pancreatitis chronic): a 58-year-old Caucasian male has a history of chronic ongoing pancreatitis with a diagnosis date that precedes cenobamate treatment by

approximately 2 months. On study day 1 cenobamate was discontinued after a single dose of 12.5mg. On study day 35 the patient experienced an exacerbation of chronic idiopathic pancreatitis and was hospitalized. The patient presented in the emergency room with abdominal pain, possibly intermittent chronic pancreatitis. Evaluation was not contributory; the patient was discharged on the second hospital day on a proton pump inhibitor. *Causal Assessment: This event is not related to cenobamate. The single dose occurred over one month before the episode of abdominal pain.*

YKP3089C021- (b) (6) (PT vomiting): a 23-year-old Caucasian female experienced a seizure accompanied by a fall and head injury on study day 55. The patient had a severe headache and vomited. There was no treatment at the hospital and the patient was discharged on study day 57. Cenobamate was increased from 100mg to 150mg on study day 56. The patient continued cenobamate until C021 study day 453, reaching a dose of 350mg (ex.xpt dataset). *Causal Assessment: This adverse event of vomiting is due to sequelae of a breakthrough seizure, no causally related to cenobamate.*

Skin and Subcutaneous Disorders

YKP3089C021- (b) (6) (PT rash papular): a 42 yo Caucasian male developed mild erythematous papular rash (abdomen and proximal lower limbs) on study day 316 at a Cenobamate dose of 400mg. Dermatologist examination: the subject presented with papular eruption of bilateral flank progressing to proximal lower limbs. The rash was not itchy, the subject was systemically well and there was no mucosal involvement. No personal or family history of dermatological conditions. Physical exam and laboratory revealed no evidence of other hypersensitivity signs or symptoms. Cenobamate was discontinued on study day 337.

YKP3089C021- (b) (6) (PT rash papular): a 32 yo Caucasian female. On study day 138 on a cenobamate dose of 150mg, the subject developed mild ERYTHEMATOUS RASH (PAPULAR) considered serious by the investigator due to important medical event. The subject called the site on study day 139 and informed that she took cenobamate 150 mg on study day 137 and woke up on study day 138 feeling itchy and hot. The subject voluntarily withheld study medication on study day 139 and reported that the skin reaction substantially reduced. The patient was reviewed by investigator on 139 and some mild papular erythematous rash was observed. The study drug was withdrawn due to event on 138. The patient recovered on study day 143.

YKP3089C021- (b) (6) (PT rash papular): a 21-year-old native Hawaiian or other Pacific Islander experienced moderate ERYTHEMATOUS RASH WITH PAPULES TO HANDS AND FEETS on study day 39 at a cenobamate dose of 50mg for 14 days. The event was assessed as serious (important medical event). The study drug was withdrawn due to the event and the last dose of cenobamate was taken on study day 38. Right dorsum skin punch biopsy showed spongiotic reaction with dermal perivascular infiltrate and eosinophilia, consistent with a drug reaction. Physical exam and laboratory revealed no evidence of other hypersensitivity signs or

symptoms. The subject was recovering from the event.

YKP3089C021- (b) (6) (PT rash): a 24-year-old Asian female developed moderate SKIN RASH on study day 33 after receiving 50mg of cenobamate daily for 10 days. The rash was further described as maculopapular rash and was spreading over the whole-body area with itching sensation. The subject was treated with oral prednisone 60mg daily and ranitidine 150mg twice daily then ranitidine was changed to Allegra 60mg daily. Cenobamate was discontinued on study day 32. The event narrative reports patient recovered 75 days after discontinuation of cenobamate. There was a small increase of eosinophils over the upper limit of normal when examined by a local laboratory on study day 34 but subsequent examination by central lab on study day 35 and 49 were within normal limits. Total neutrophil % was increased over upper limit of normal on study days 35 and 49 while leukocytes were elevated on study day 49.

YKP3089C021- (b) (6) (PT rash maculo-papular): 33-year-old Caucasian male experienced moderate ERYTHEMATOUS MACULOPAPULAR RASH, LEGS AND ARMS on study day 61 after 4 days after an escalation to cenobamate 150. The rash was further described as blotchy, red rash on right thigh. Cenobamate was discontinued on study day 61. As per the subject the rash was intensely pruritic and was spreading into his right thigh and groin. On examination by the dermatologist, there was an erythematous macular rash which was coalescing into plaques on the right hip, upper thigh and groin. There were papules and macules on the left hip; there was no oral or ocular involvement and no penile involvement. There was no increased work of breathing and no lymphadenopathy and the skin check was otherwise normal. Two punch biopsies from the right hip were performed the first revealed features consistent with an urticarial reaction. The second of the biopsies revealed mixed spongiotic and urticarial reaction, consistent with a drug reaction. The patient was treated with Betamethasone dipropionate ointment. The patient recovered from the event 22 days after cenobamate discontinuation. Recovered study day 82.

YKP3089C021- (b) (6) (PT Urticaria): a 46-year-old Caucasian female developed a moderate urticarial body rash after 2 doses of 12.5mg cenobamate. Physical exam and laboratory revealed no evidence of other hypersensitivity signs or symptoms. The study drug was withdrawn due to the event and the subject was treated with Fexofenadine and Dexchlorpheniramine. The subject recovered from the event within 1 day.

YKP3089C021- (b) (6) (PT erythema): On study day 22 after 7 days of cenobamate 25mg a 48-year-old Caucasian female experienced facial redness across cheeks, nose, chin and forehead. Study drug was discontinued on study day 28. The patient recovered 34 days after cessation of cenobamate on study day 61.

YKP3089C021- (b) (6) (PT dermatitis allergic): a 39-year-old Caucasian female experienced mild cutaneous allergy secondary rash with erythematous lesions at right gluteal region. This occurred on study day 66 at a cenobamate dose of 100mg. Cenobamate had been advanced to 100mg ten days prior to onset of the erythema. Three days later on study day 69 the

cenobamate dose was advanced to 150mg. Two day later the patient noted lesions o abdominal thoracic area with no other signs or symptoms. Hematology, biochemistry, renal and hepatic in blood without any significant abnormality. Cenobamate was discontinued on study day 86 after reduction from 150mg to 50mg on study day 83 (ex.xpt dataset). The patient is reported to have recovered from the event on study day 104.

YKP3089C021- (b) (6) (PT swelling face): 32-year-old Caucasian male experienced moderate lip swelling on the second day of cenobamate 12.5mg treatment. The patient went to the emergency room where no lymphadenopathy, respiratory or other signs were present. Hematology, liver transaminases and the rest of the blood tests along with the vital signs were normal. Cenobamate was discontinued on study day 2. The swelling resolved in less than 24 hours.

Summaries From the Category of "Less than 9 entries with Outcome 'Resolved with sequelae'"

YKP3089C021- (b) (6) (PT Laryngospasm): this is a report of a 21 yo female with Angelman syndrome with a fatal outcome that is discussed in [Section 8.4.1](#).

YKP3089C021- (b) (6) (PT pulmonary embolism): a 59 yo Caucasian male experienced a bilateral pulmonary emboli on day 373 of cenobamate treatment at a dose of 200mg. The patient was treated with the 200mg dose for three months. Th patient was discovered to have a D-dimer elevation of 1.54 as an outpatient. The case narrative identifies onset of a prior pulmonary embolism (PE) ongoing since 2/4/18. The patient began cenobamate treatment on 2/9/17. There is no entry in adverse event dataset of a prior PE. The record indicates the patient was taking Eliquis 5mg twice a day beginning 2/4/18. The patient has morbid obesity with a BMI of 42.5. The patient presented to the emergency room on study day 373 with acute dyspnea. A cT pulmonary angiogram showed extensive pulmonary embolisms bilaterally with a large clot load and evidence of new deviation the IV septum consistent with right heart strain. The subject was initially treated with Lovenox and per subject's request was started on rivaroxaban. The subject previously had a pulmonary embolism that was treated with apixaban and developed a rash so the apixaban was stopped to trial off anti-coagulation. The patient improved, cenobamate dose was not changed. The patient was discharged back to an assisted living facility on study day 378 on treatment with rivaroxaban a minimum of 6 months. No cause for the PE was determined. *Causal assessment: The occurrence of spontaneous pulmonary emboli is of concern due to the potential pro-hypersensitivity properties of cenobamate that could be active in the background to produce a inflammatory environment. Pro-inflammatory states are a risk factor for venous thromboembolism. In this case the causality is confounded by the morbid obesity and concurrent metabolic syndrome that are also pro-inflammatory. The background physical activity of the patient is also uncertain and may be compromised. This is likely since the patient resides in an assisted living facility at an earlier age than typical.*

YKP3089C021- (b) (6) (PT Atrioventricular block complete): this 65 yo Caucasian female developed complete heart block and deep vein thrombosis and was admitted to the hospital on study day 185. of incomplete compressibility involving the popliteal vein, compatible with occlusive thrombus. The subject was diagnosed with deep vein thrombosis (DVT) and treated with Eliquis (apixaban). On study day 185 the subject had an episode of seizure and bradycardia. Cardiovascular testing included EKG, which showed sinus rhythm with no ST-T abnormalities, and poor R-wave progression. Telemetry revealed sinus rhythm with ventricular standstill and agonal junctional escape rhythm with pauses up to 5 seconds. The event is confounded by lacosamide that may cause AV block. A temporary pacemaker was placed. The study drug was not changed. The patient is identified as recovered on study day 192. The exposure dataset indicate the patient continued with cenobamate treatment in study C021 until day 448 on a dose of 250mg. This event is confounded by concomitant lacosamide. Causal relationship of the AV block to cenobamate is uncertain. *Etiology of the DVT is uncertain, causal relation to cenobamate cannot be excluded due to the absence of an alternative etiology.*

YKP3089C021- (b) (6) (PT squamous cell carcinoma): This 57 yo Caucasian female had a diagnosis of a right mandible squamous cell carcinoma on study day 336 while receiving 250mg of cenobamate. The identification of this event was preceded by worsening right facial swelling for one month. The patient reported having teeth extracted 1.5 months prior to the diagnosis and had facial pain since that time. This was initially treated unsuccessfully as possible infection. imaging study showed a large infiltrative soft tissue mass centered in the right masticator space/buccal space with through and through erosion of the right mandibular body, ramus, and coronoid process with extension into the right parapharyngeal space measuring at least up to 7.3 cm in size. Findings were highly suggestive of aggressive neoplasm rather than infection. Pathology report confirmed invasive squamous cell carcinoma of the right mandible. Additionally, there was a large partially necrotic right cervical lymphadenopathy, worrisome for metastases. *Causal relationship to cenobamate unlikely but cannot be completely excluded. The 336-day exposure appear insufficient to allow development of a large malignant mass; however, an aggressive histology may advance rapidly.*

YKP3089C021- (b) (6) (PT pelvic mass): On study day 48 this 61 yo African American female was found to have a benign abdominopelvic mass. This was a multiseptated complex right ovarian mass measuring 12.7 cm associated with postmenopausal bleeding. Tumor markers were not positive. On study day 48 the patient underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy with omental biopsy, the frozen path was benign. *This mass is not causally related to cenobamate.*

YKP3089C021- (b) (6) (PT Cholelithiasis): 39 yo African American female developed severe symptomatic cholelithiasis on study day 200 while treated with 350mg of cenobamate. The patient presented with right flank and right upper quadrant pain. This lesion occurs on a background of morbid obesity and type II diabetes. The patient is treated with insulin for her type 2 diabetes. The patient underwent laparoscopic cholecystectomy and adrenalectomy of a

nodule. During hospitalization on study day 211 the patient developed a pulmonary embolism. Pathology report of the gallbladder, cholecystectomy: Chronic cholecystitis and cholelithiasis. Adrenal gland, left, resection: adrenocortical neoplasm, favor adrenal adenoma (tumor measures 5.2 cm in greatest dimension). It was noted that the adrenal cortical neoplasm lacked histologic features that have been associated with an aggressive behavior, such as increased mitotic activity, atypical mitoses, high nuclear grade, low percentage of clear cells, necrosis, diffuse tumor architecture, capsular invasion and sinusoidal/venous invasion. Taken together, the histologic findings favor a diagnosis of adrenal cortical adenoma. The subject was treated for the pulmonary embolism with enoxaparin 1 mg/kg every 12 hours. Lifelong anticoagulation was anticipated. The pulmonary emboli were judged to be a late complication of the subject's recent abdominal surgery. The study drug was not changed and the exposure dataset reveals the patient was treated with cenobamate 350mg in study C021 until day 428 with an increase to 400mg from day 429 to 461. *Causal relationship of the cholelithiasis to cenobamate is not concluded. The patient is in a high-risk cohort for cholelithiasis. Causal relation between cenobamate and the adrenal nodule is unlikely. The module 2, non-clinical overview does not identify a carcinogenic potential. In addition, induction of a malignant transformation and generation of a nodule in 200 days of exposure is also unlikely. The pulmonary embolism is a likely complication of the surgery and high-risk body habitus.*

YKP3089C021- (b) (6) (PT Chest Pain): this 48 yo African American female developed severe chest pain on study day 44 while treated with 50mg of Cenobamate. ECG showed normal sinus rhythm with no ST-T abnormalities Treadmill stress test was unremarkable. Troponin was negative as well as a proBNP. Cenobamate was discontinued on study day 45. Cardiac studies related to electrophysiologic, and ischemic heart disease did not reveal an abnormality. *Causal relationship to cenobamate is not supported.*

YKP3089C021- (b) (6) (PT cholecystitis acute): 40 yo Caucasian female developed acute calculous cholecystitis on study day 324 while treated with 200mg of cenobamate. subject experienced the severe SAE of acute calculous cholecystitis and was hospitalized. The subject presented to the emergency room with sharp right upper quadrant abdominal pain associated with nausea, no vomiting. Physical examination revealed some tenderness in the right upper quadrant, with no guarding or rebound. The gallbladder was prominent with large amount of sludge and several stones seen, some pericholecystic fluid and slight gallbladder wall thickening present. The common bile duct was dilated at 8mm. A laparoscopic cholecystectomy with cholangiography was performed on study day 324. Findings revealed an edematous gallbladder with thickened wall and no hydrops. The study drug was not changed as a result of the event of acute calculous cholecystitis. *Causal relationship to cenobamate cannot be excluded because all physiologic effects of a new chemical entity are not known. However, the presence of sludge in the gall bladder is likely the result of a chronic process.*

YKP3089C021- (b) (6) (PT sudden death): this patient is identified in [Section 8.4.1](#) above as a case of SUDEP.

YKP3089C021- (b) (6) (PT pulmonary embolism): 18 yo Caucasian male had an SAE of seizure exacerbation on study day 130 and was hospitalized. The patient suffers atonic seizures. During the hospitalization for seizure exacerbation the patient received enoxaparin for venous thrombosis prophylaxis. Later on study day 182 while taking 300mg cenobamate the patient developed an acute pulmonary embolism and was hospitalized. The patient presented with right pleuritic chest pain. A CT pulmonary angiogram on the same date revealed findings in keeping with an acute pulmonary embolus within a segmental pulmonary artery within the right lower lobe. Moderate volume right-sided pleural effusion. The subject was treated with Clexane (enoxaparin). The management plan included rivaroxaban 15 mg orally twice a day for 21 days, then 20 mg orally daily, follow-up with epilepsy clinic. The study drug was not changed due to the event. Based on the exposure dataset the patient continued treatment with cenobamate in study C021 until study day 364. *Causal relation between the pulmonary embolism and cenobamate cannot be excluded. An alternative etiology was not identified.*

YKP3089C021- (b) (6) (PT serositis): 45 yo Caucasian male with past medical history of chronic myeloid leukemia and concomitant treatment with dasatinib, developed serositis on study day 139. The patient was hospitalized. The hospital discharge summary states that the patient had been feeling non-specifically unwell over several months, possibly after starting cenobamate. The subject felt tired, often needing to nap during the day. During the week prior to hospitalization the subject complained of dry cough, lethargy, anorexia, night sweats, fevers and chills. Additionally, the subject presented with pleuritic type chest pain and a pericardial rub. An ECG revealed T wave inversion. A chest x-ray showed a small right-sided pleural effusion. An echocardiogram showed normed left ventricular size and function, normal valvular function, and small pericardial effusion. Cenobamate was discontinued on study day 139. Clinical laboratory values, from the hospitalization, also on study day 139, included the following: C. Reactive Protein which peaked at 282.6 mg/L (reference range less than 3.0), on (b) (6), ESR 104 mm/h (reference range less than 11), hemoglobin 8.7 g/dL (reference range 12 – 18), ferritin 586 mcg/L, iron 8.6 umol/L (reference range 10.0 –80.0), transferrin 1.64 g/L (reference range 2.10 – 8.00), abnormal liver function tests (ALP 246, GGT 846 U/L, mild elevation of transaminase levels), and a positive ANA titer at 640 (connective tissue screen otherwise negative). HIV serology negative, Hepatitis B and C serology negative and EB virus and CMV virus negative. Outpatient lab test results on study day 148, 8 days after cessation of cenobamate and dasatinib, revealed subject's hemoglobin improved to 10.9 g/dL, ESR decreased from 110 to 95 mm/h over one week, and the CRP was down to 84.3 mg/L, normal renal function, ALP improved from 191 on (b) (6) to 142 U/L and GGT improved from 663 U/L to 475 U/L. After the discontinuation of cenobamate and dasatinib, the subject was reported to improved clinically. Causal relationship of this serositis is confounded by treatment with dasatinib. Dasatinib has an entry in W&P for severe dermatologic reactions as well as a signal for serositis in Section 6, Clinical trials experience where pleural effusion and pericardial effusion are seen as adverse reactions. An examination of dasatinib in Empirica signal reveals an EB05 of 2.56 for polyserositis. *Causal Assessment: causal relationship to cenobamate is confounded by concomitant therapy with dasatinib, a drug with established signal for serositis.*

YKP3089C021- (b) (6) (PT Hypovolemic shock): This patient was fatally injured when struck by a motor vehicle. See [section 8.4.1](#).

YKP3089C021- (b) (6) (PT uterine leiomyoma, endometriosis): 44-year-old Caucasian female developed metrorrhagia with heavy bleeding and abdominal pain on study day 116. This occurs on a background of a two-year history of heavy, continuous and irregular menstruations. On study day 127 the subject experienced the severe SAEs of myoma and external genital endometriosis worsening and was admitted to the hospital for scheduled surgical treatment. On study day 130 the patient underwent a total laparoscopic hysterectomy with bilateral salpingectomy. The study drug was not changed due to the events. *Causal Assessment: No support for causal relationship to cenobamate. Event due to pre-existing condition.*

YKP3089C021- (b) (6) (PT Intervertebral disc protrusion): 43 yo Caucasian female had diagnosis of massive disc extrusion with herniation at L4/L5 to the left with compression of nerve root. On study day 112 the patient underwent decompression of roots and dural sac L4/5 on the left, and sequestrectomy. The postoperative course was uneventful, standing up since day 1 after surgery, rehabilitation with active therapeutic exercises, walking. Subjectively no radicular pain, felt well, neurology objectively without accentuation of a mild motor deficit in L5 on the left, no urine disorder. Wound healed. Cenobamate treatment was not changed. *Causal Assessment: There is no support for causal relationship to cenobamate. This event was due to pre-existing condition.*

YKP3089C021- (b) (6) (PT Arterial haemorrhage): 26-year-old Caucasian male. This patient has a past medical history of Tetralogy of Fallot, an MCA infarct, reconstructive cardiac surgery. Concomitant medications included: acetylsalicylic acid 100 mg oral once a day for prophylaxis of left middle cerebral artery infraction, ongoing since (b) (6). On study day 292 the subject experienced the severe SAE of left thoracic artery bleeding and was hospitalized. bronchoscopy revealed hemorrhage visible in the left S3 segment which lessened with local hemostasis. On study day 294, an acute thoracic CT confirmed an abscedating process in the S3 and the aberrant vessel structure also arose as the origin of the hemorrhage. C-reactive protein was elevated at 34.4 and the patient again became pyretic, and therapy was changed to Tienam and Avelox combination. Abscedating pneumonia and pulmonary hypertension were considered the underlying causes of the massive hemoptysis. The study drug was not changed due to the event. The patient continued treatment with cenobamate until study day 348. *There appears to be no causal relation to cenobamate treatment.*

YKP3089C021- (b) (6) (PT hyponatremia): 20-year-old Hispanic male developed hyponatremia on study day 379 and was hospitalized. The patient had dizziness and nausea since starting cenobamate and the patient was in the process of down titration. On the day of admission, the subject had abdominal pain with dizziness and one episode of vomiting. On study day 379 (day of admission), abnormal laboratory test results included glucose 121 mg/dL, sodium 127 mmol, chloride 94 mmol, creatinine 0.63 mg/dL, alkaline phosphatase 115 IU/L. ECG revealed normal sinus rhythm. NSS 0.9% was started intravenously. Study drug was

discontinued. The patient was discharged the following day. *Causal relationship to cenobamate is unlikely due to absence of temporal relationship and the possibility of a temporal relation to vomiting. An SIADH effect cannot be excluded.*

Reports (of interest) not Captured by Variable "AEACN, "AEREL" and "AEOUT" Criteria.

YKP3089C021- (b) (6) (PT Fibrin D dimer increased): 22-year-old African American male had 8 seizures on study day 25 while on 25mg of cenobamate. Laboratory abnormalities obtained included increased creatinine, BUN, and decreased creatinine clearance with values of 3.3mg/dl, 35mg/dl and 35mg/dl respectively. Follow up measurement of these values on study day 29 show improvement. The subject was treated with intravenous fluids, acetaminophen, polyethylene glycol powder, pregabalin, lidocaine viscous mucous membrane liquid, and eslicarbazepine. This patient later had a left fibular fracture/trimalleolar fracture of ankle associated with alcohol intake. On study day 406 on a cenobamate dose of 200mg the patient had an event of carpopedal spasm with a laboratory abnormality of markedly elevated D-dimer (10,229-units and reference range not provided) identified. The subject presented (day 406) with 3 weeks of cramping and tingling and generalized weakness in the setting of stopping medications and alcohol abuse. He reported chronic symptoms of fatigue and pain related to his underlying health problems. The basis for the elevation of D-dimer was not identified. There was no evidence of venous thrombosis or pulmonary embolism. Examination of scheduled laboratory measurements on study days 357 and 532 reveal a low phosphate (1.8 meq/L, low reference range 2.5) , mild reduction of potassium (3.4meq/L) and low absolute neutrophils ($1.3 \times 10^9/L$, low reference range 1.7) on study day 357. These abnormalities are not associated with carpopedal spasm. Serum creatinine, BUN and creatinine are examined at all 13 scheduled study visits to determine if the abnormality on study day 25 represents a chronic kidney injury. The only abnormality of these parameters is observed on study day 27 (visit 4) where creatinine was 3.3mg/dl (normal 0.7-1.4), blood urea nitrogen (BUN) was 35 mg/dl (normal 5-20) and creatinine clearance was 35mL/min (normal 85-125). Values for these parameters were normal in all preceding and the remaining 10 measurements over the subsequent 505 days the patient participated in study C021. *Causal assessment: The event of elevated creatinine appears to be a sporadic event, possibly related to a period of acute dehydration. The elevated D-dimer is without explanation but may have been an acute phase response related to the event of carpopedal spasm. Assessment of this patient's medical status is confounded by evidence of alcohol abuse. There is no support for causal relationship to cenobamate.*

YKP3089C021- (b) (6) (PT Acute respiratory failure): 21-year-old Caucasian female with Angelman syndrome. This patient had severe medical compromise and is discussed in [Section 8.4.1](#).

YKP3089C021- (b) (6) (PT Pyrexia): 21-year-old Caucasian male experienced the serious adverse event of fever of unknown origin on study day 449 while taking 250mg cenobamate

(dose escalated on study day 266). This finding occurred in the context of a seizure cluster. The patient body temperature in the emergency room was 102F. The event resolved and no cause for the fever or seizure cluster was identified. *Causality assessment: Cenobamate cannot be excluded but the episodic characteristic and absence of temporal relationship to initiation or a dose escalation makes a causal relationship very unlikely.*

YKP3089C021- (b) (6) (PT visual acuity reduced): 43-year-old Caucasian female (country Poland) with diagnosis of epilepsy at age 12 and a history of left parietal lobe brain tumor at age 18. On study day 350 the patient had “weakness of visual acuity” and was hospitalized in the ophthalmology ward for observation. The patient also reported about one year of periodic headache and “weakness of visual acuity”. Technical details of the ophthalmology are provided but normal values are not provided. It can be inferred there is no glaucoma, visual scotoma. A gonioscopic exam was performed and apparently a fluorescein angiography study but results are not provided. Visual acuity is not reported. The patient was discharged to have follow up with treating physician, cenobamate was continued but the exposure dataset reveals the last day of treatment in study C021 was day 353. *Causal assessment: This cannot be determined at this time because the visual lesion is unclear, and a diagnosis is not provided. This may be due to background migraine headache or a remote effect of the parietal lobe tumor, but this is speculative.*

YKP3089C021- (b) (6) (PT breast cancer): 60-year-old Caucasian female had a diagnosis of breast cancer on study day 85 while taking 200mg of cenobamate, identified during a routine screen. On study day 163 the patient had an additional SAE of balance disorder. This was found to be associated with concomitant carbamazepine dose. *Causality assessment: the short latency between initiation of cenobamate and diagnosis of breast cancer of less than 2 months does not plausibly support a causal relationship.*

YKP3089C021- (b) (6) (PT Acute myocardial infarction): This 38-years-old Spanish, Caucasian female suffered an acute myocardial infarction study day 170 while taking 300mg of cenobamate. There was a positive troponin I at 1.19 ng/ml, reference range not provided. Further history reveals the patient had first cardiac symptomology at approximately study day 80. This pain is characterized as an episode of oppressive pain in the center of the chest, radiating to the arms, jaw and back. The pain was intense and associated with autonomic symptoms, occurring after moderate effort and lessening on its own with rest. This occurs on a background of light cigarette smoking, positive family history of ischemic cardiopathy (mother had AMI at age 50) and a medical history of dyslipidemia. Cenobamate treatment was continued in study C021 until study day 450. *Causal assessment: A role of cenobamate cannot be excluded however is rendered less likely by a strong family history of early coronary disease, smoking and medical history of dyslipidemia.*

13.3. DRESS Case Narratives

Study C018

Patient 13 (1 of 3 Adjudicated DRESS Cases)

50-year-old White male) in Cohort 2 began to experience warmth to the trunk and developed a diffuse erythematous rash to the trunk, arms, and legs (bilaterally) on Day 14 (b) (6) approximately 5.4 hours after receiving the 4th dose of 400 mg YKP3089. He received therapy of oral diphenhydramine hydrochloride that day. The subject was examined by the PI the following morning and found to have a diffuse erythematous rash to trunk, arms and legs that was very red and pruritic. The subject denied any difficulty swallowing or breathing and dosing was continued. That evening he again received oral diphenhydramine for complaint of pruritus. Later that evening, he also complained of feeling weak. Over the next 6 days the rash showed little improvement and the subject complained of continued itching, for which he was treated with oral diphenhydramine 50 mg.

On Study Day 22 (b) (6) the rash was noted to include the palms of the hands and soles of the feet. No stridor was noted, and there was no uvular or tongue swelling; the subject denied difficulty swallowing and was allowed to dose. Later that same day, the subject began to complain of tightness of facial skin and was noted to have soft facial tissue swelling as well as swelling of the digits bilaterally. No swelling of the lips or oral mucosa was noted. At this point the decision was made by the PI to discontinue dosing and keep the subject domiciled in the clinic for safety. The subject received the last dose of 500 mg YKP3089 on Day 22. The subject received a total of 5 doses each of 200, 300, and 400 mg YKP3089 and 7 doses of 500 mg YKP3089 before the study drug was discontinued.

On Day 23 (b) (6) in the morning, the subject had increased weakness; stating that it was difficult to get out of bed. The rash remained present and the subject continued to deny any difficulty breathing or swallowing. That afternoon, he began to have swelling of the lips and bilateral eyelids, body aches, and a burning sensation in the areas covered by the rash. He received oral diphenhydramine, oral paracetamol, and topical hydrocortisone. Vital signs were normal with the exception of a pulse rate of 99 bpm at a single time point. That evening, his oral temperature increased to 103.8°F, accompanied by a pulse rate of 106 bpm. He was given oral paracetamol.

On Day 24 (b) (6) the subject again had an increased temperature, with a maximum of 103.2°F, and increased heart rate of 106 bpm. He received oral diphenhydramine and paracetamol. The pruritic rash was still present. He had continued weakness with observed difficulty changing positions in bed. He reported feeling achy all over, with moderate pain to entire body. He also was noted to have generalized pustules over his face and increased swelling to the facial soft tissues. The subject was given intramuscular methylprednisolone sodium succinate.

Laboratory work was performed and abnormal laboratory results of note at this time were as follows: sodium 122 mEq/L (reference range 133 - 145 mEq/L), chloride 88 mEq/L (reference range: 97 - 105 mEq/L), blood urea nitrogen (BUN) 28 mg/dL (reference range: 6 - 20 mg/dL), creatinine 1.70 mg/dL (reference range: 0.8 - 1.3 mg/dL), bicarbonate 21 mmol/L (reference range 24.2 - 33.6 mmol/L), ALT 517 U/L (reference range 11 - 65 U/L), aspartate aminotransferase (AST) 173 U/L (reference range: 15 - 46 U/L), GGT 255 U/L (reference range 7 - 62 U/L), white blood cells (WBCs) 13.8 Thou/ μ L (reference range: 3.4 - 10.5 Thou/ μ L), lymphocytes 8.6% (reference range: 16.8 - 51.7%), neutrophils 84.0% (reference range: 40.2 - 75.0%), and absolute neutrophil count (ANC) 11.6 Thou/uL

(reference range: 1.5 - 7.0 Thou/L). Glomerular filtration rate (GFR), while still within normal limits at 66 mL/min (reference range: > 60 mL/min), was significantly lower than at baseline (125 mL/min). The decision was made to transfer the subject via ambulance to the local emergency room.

At the hospital, initial blood work was consistent with the findings at the site. Additional findings included albumin 2.5 g/dL, calcium, 7.8 mg/dL, and INR 1.41. In addition, 2 blood cultures revealed Staphylococcus Epidermidis. Treatment with Vancomycin 1 g QD was initiated along with normal saline, heparin, and Solu-Medrol® 120 mg /day.

The subject was seen by an infectious disease physician. Vancomycin was discontinued by the infectious disease physician who believed, based on the lack of corroborating symptoms, that the blood cultures were contaminated. The infectious disease physician believed the diffuse maculopapular rash was likely a drug eruption secondary to an antiepileptic drug. Within 24 hours, the patient showed signs of clinical improvement with less fever, feeling stronger and some resolution of the rash. Renal function improved, WBC counts reduced with normalization of granulocytes and calcium increased. Hepatitis panel for A, B and C was negative. However, on 30 January 2013, AST increased to 568 U/L, ALT increased to 809 U/L and alkaline phosphatase increased to 133 U/L.

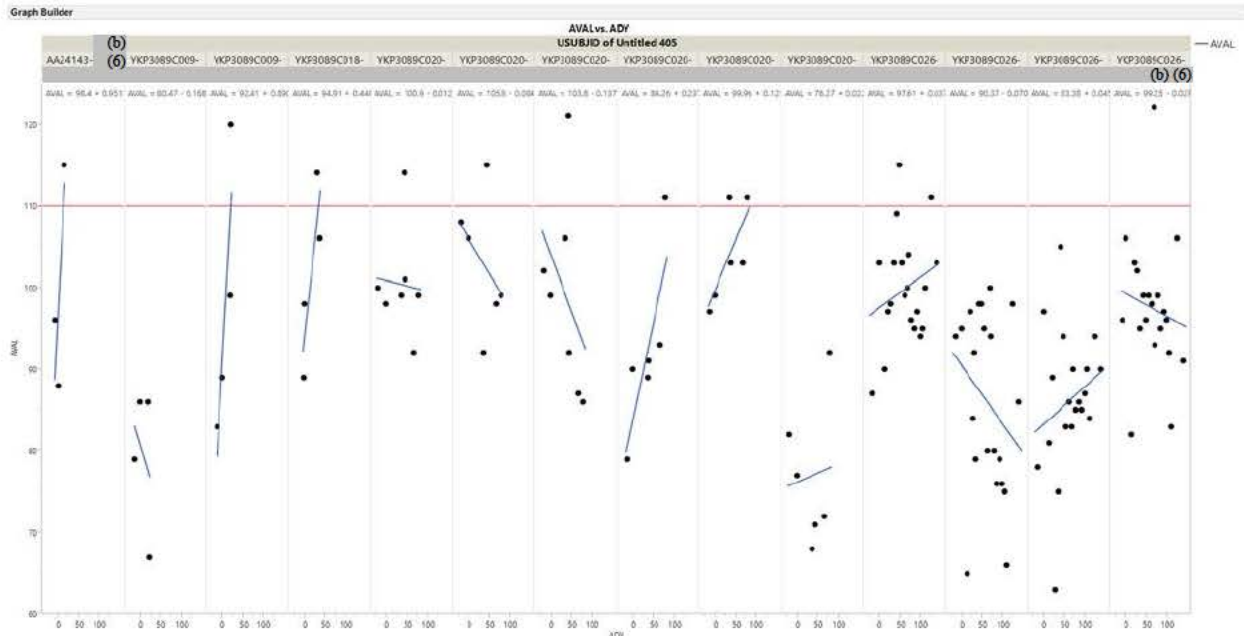
On (b) (6) a dermatologist reported a diffuse dusky discoloration of skin involving hands and feet plus areas of fine scaling and palpable purpura extensive on legs. His first impression was drug hypersensitivity syndrome including systemic symptoms and leukocytoclastic vasculitis. A CBC with differential ordered by the dermatologist revealed eosinophils of 11% with a total WBC of 7.1 Thou/ μ L. Based on the elevated eosinophil count, the dermatologist believes the condition of the subject can best be characterized as a DRESS syndrome. By (b) (6) the rash was resolving, and the liver and kidney functions tests were returning towards normal.

By discharge from the hospital, the sodium, chloride, BUN, creatinine, bicarbonate, and WBC count were within normal limits. The ALT and AST were still elevated but trending downwards. Hemoglobin level was still low at 11.5 g/dL (reference range 12.6 - 16.8 g/dL) as was albumin at 2.7 g/dL (reference range 4 - 5.2 g/dL). The subject was alert and oriented, in stable condition, and his symptoms had significantly improved. The subject was discharged from the hospital on (b) (6) and returned to the clinical site. The subject continued to follow up with the clinic until resolution of his symptoms. Safety labs drawn on (b) (6) showed that the international normalized ratio (INR), which was elevated during hospitalization to 1.41 (reference range: 0.9 - 1.1) and AST were now within normal limits and the GFR had improved back to baseline at 113 mL/min. Safety labs drawn on 21 February 2013 showed that hemoglobin and albumin were within normal limits and that GGT and ALT were only slightly elevated. The symptoms of itching and rash continued to improve per follow-up phone calls by the subject. The SAE was considered resolved on (b) (6)

13.4. Phase 1 Chemistry

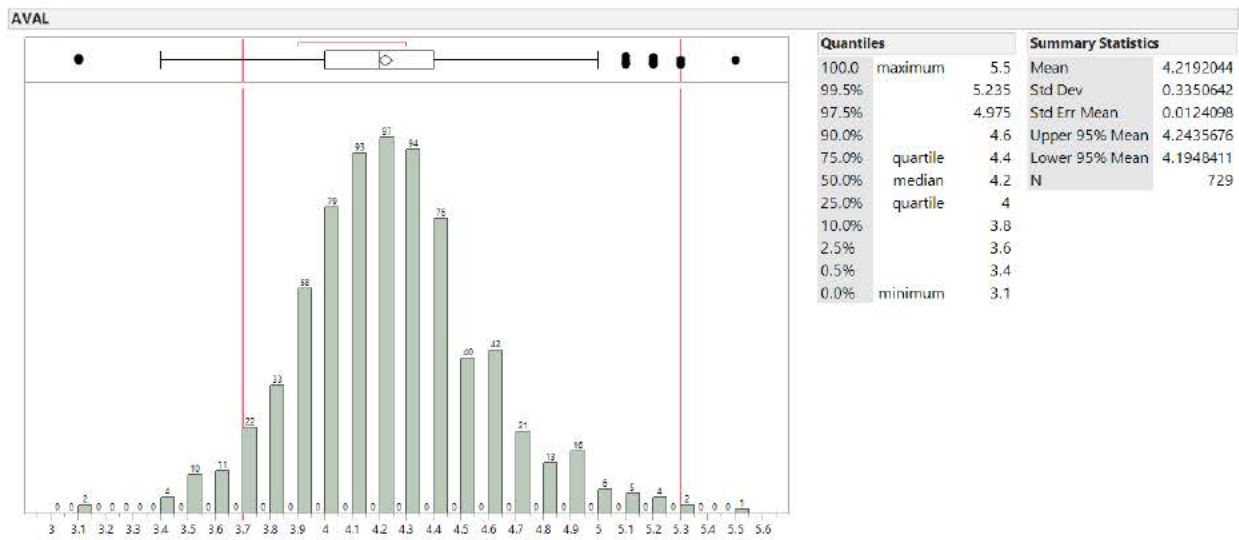
13.4.1. Glucose

Figure 88 Phase 1 Subjects with any Post-baseline OORR – high or OORR – low value, Full Study Trendline

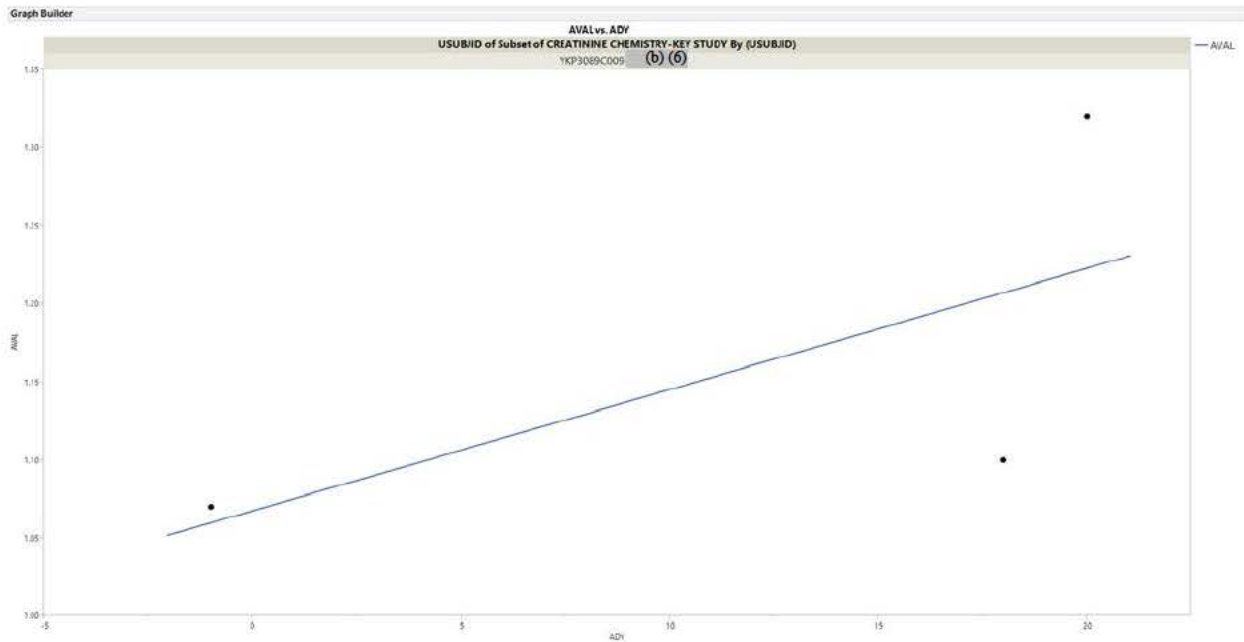
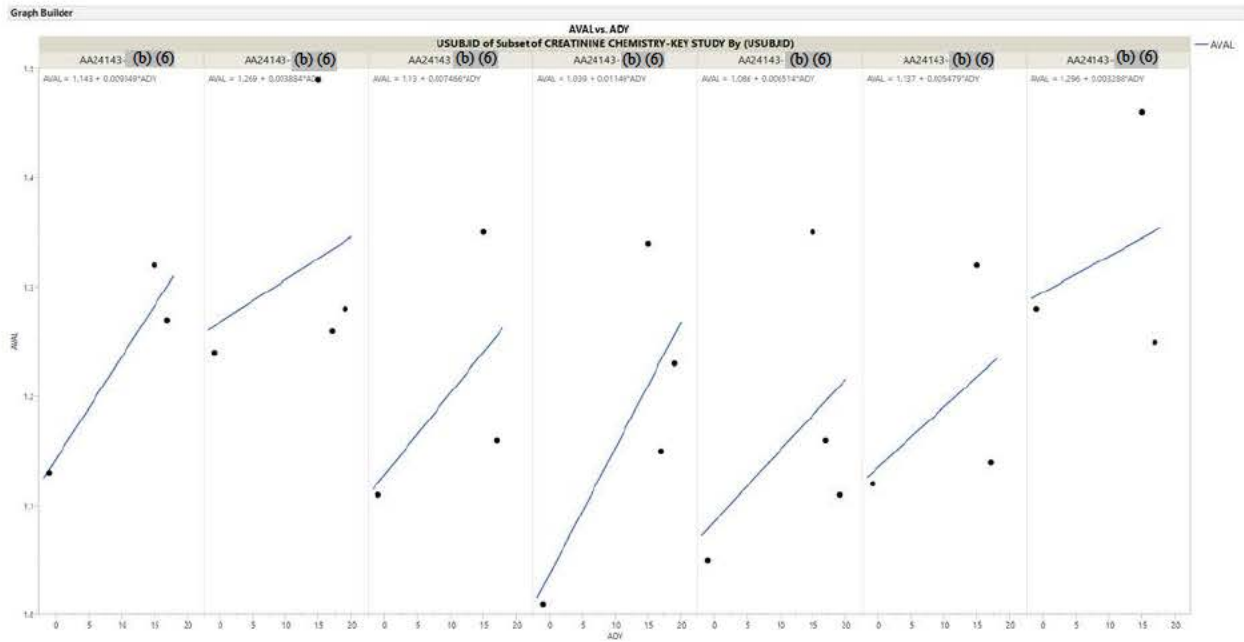


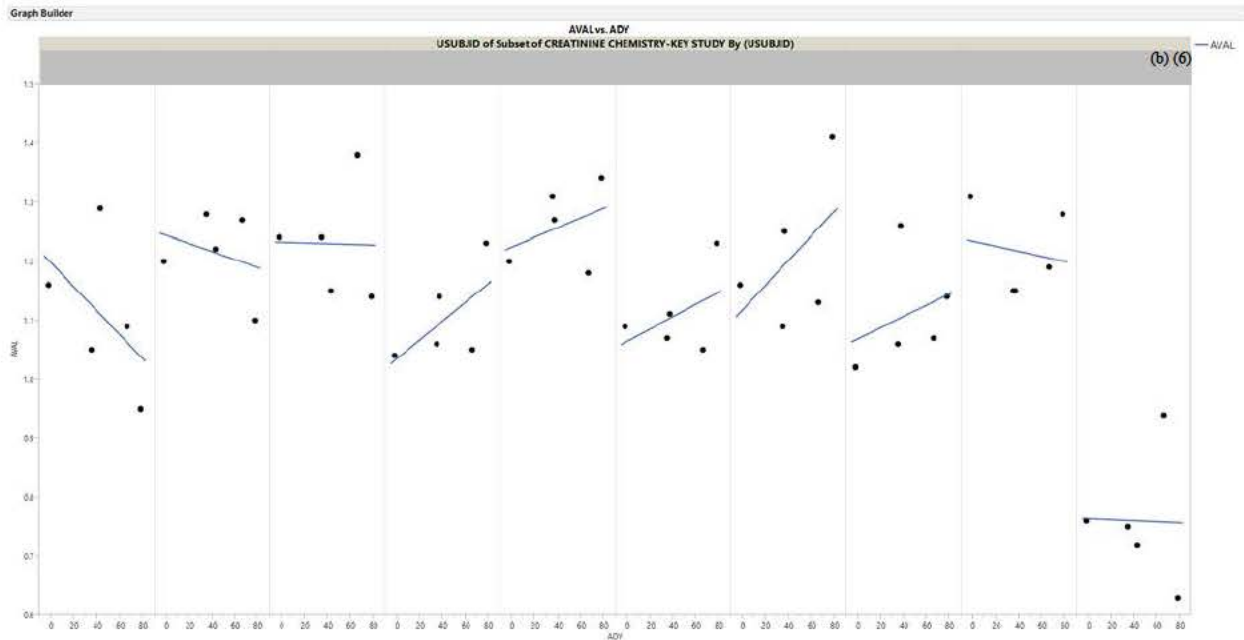
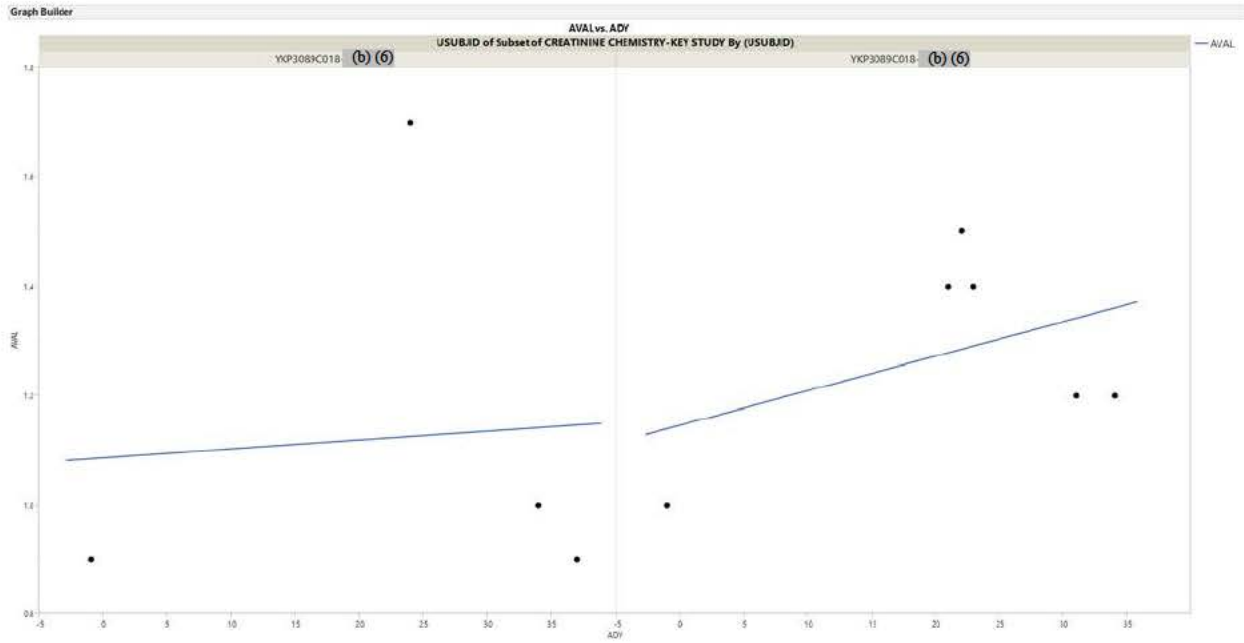
13.4.2. Potassium

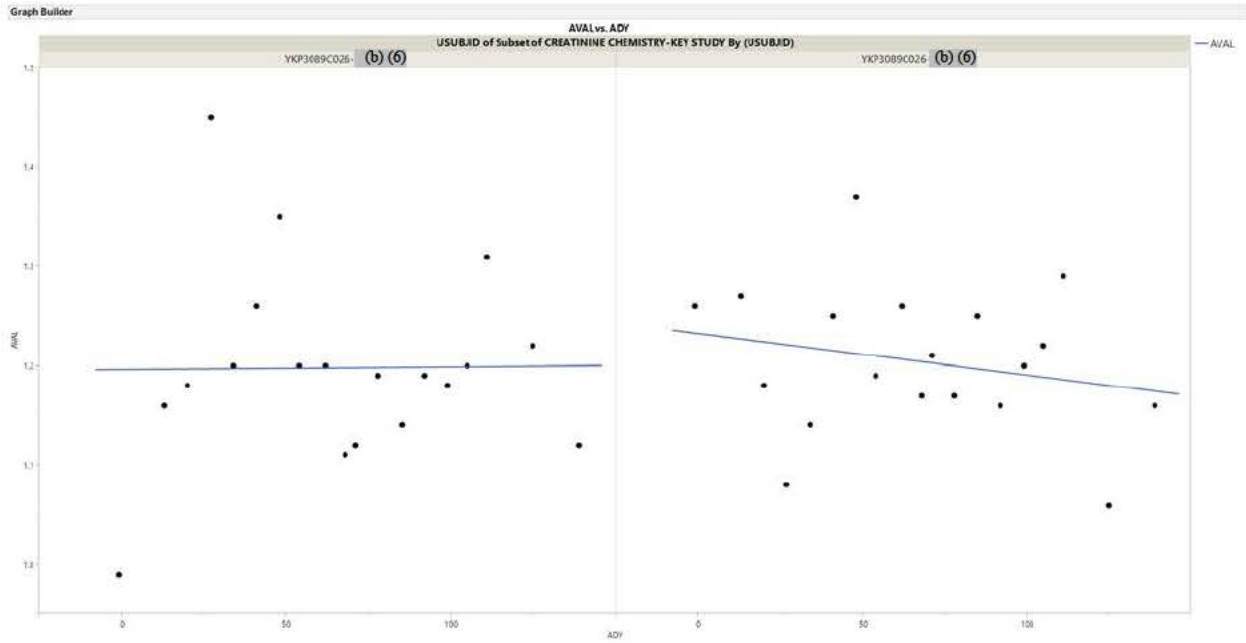
Figure 89 Phase 1 Distribution of Post-Baseline, On Treatment Potassium Values



13.4.3. Creatinine Elevation Profiles by Patient of Interest







This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEVEN T DINSMORE
11/21/2019 10:32:48 AM

PHILIP H SHERIDAN
11/21/2019 10:37:34 AM

CLINICAL REVIEW

NDA number	212839
Application holder	SK Life Science, Inc.
Drug	Cenobamate
Topic	DRESS
Medical reviewer and Office/Division	Gerard Boehm, MD, MPH ODE I, DNP

DRESS Background

Drug reaction with eosinophilia and systemic symptoms (DRESS), also referred to as Drug induced hypersensitivity syndrome (DIHS), is a hypersensitivity reaction involving multiple organ systems and characterized by rash, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver dysfunction. I include several diagnostic criteria proposed for DRESS as appendix A to this review. Onset of DRESS symptoms generally occur 2-8 weeks after initiating a drug. DRESS has been reported with drugs such as carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, mexilitene, salazosulpyridine, allopurinol, and minocycline. DRESS is also associated with reactivation of herpes viruses (ex. HHV-6 and CMV). Estimates of DRESS risk with first or second prescription of an aromatic antiepileptic range from 2.3-4.5 in 10,000. Mortality from DRESS has been estimated to be 2-14%.¹

Several antiepileptic drugs cause DRESS and their package inserts describe these events in Warnings or Warnings and Precautions statements. Even those antiepileptic drugs with boxed warnings for other adverse events (Tegretol, Depakote, and Lamictal) do not include DRESS within the box. I include as appendix B to this review examples of the labeling language for antiepileptic drugs that cause DRESS.

Cenobamate DRESS Background

SK Life Science, Inc. (SKLSI) developed Cenobamate for the treatment of partial onset seizures. During early clinical trials, 3 cenobamate exposed participants developed DRESS and one of the cases was fatal. At the time of the identification of these cases, 833 patients took at least 1 dose of cenobamate, yielding a DRESS risk of 0.36% (3/833).

2 of the 3 cenobamate DRESS cases occurred in healthy volunteers participating in clinical pharmacology studies and the third case involved an epilepsy patient enrolled in a phase 2 trial (017). SKLSI provided narratives for the 3 DRESS cases and the clinical details and test results supporting the DRESS diagnoses. I provide brief summaries of the cases below, with detailed narratives included as appendix C to this review.

¹ Watanabe, H. Recent Advances in Drug-Induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms. *J Immunol Res* 2018 Mar 18;2018:5163129.

In the first case, a healthy 38-year-old Hispanic female who enrolled in a QT study developed a rash on day 32 and study drug was stopped the next day. Cenobamate dosing for this individual in this study was Days 1 to 7: 50 mg QD; Days 8 to 14: 100 mg QD; Days 15 to 21: 150 mg QD; Days 22 to 35: 200 mg QD. During follow up she developed pruritis, diffuse adenopathy, depressed mood, facial swelling, blurred vision, ecchymoses, chest pain, dyspnea, and palpitations. She experienced lab abnormalities including decreased hemoglobin, and elevated transaminases, bilirubin, eosinophils, and lymphocytes. She was evaluated by a dermatologist, hepatologist, internist, and study clinic staff. She had a skin punch biopsy that was consistent with DRESS. She was treated with topical, oral, and intravenous steroids and antihistamines. She was hospitalized twice. On study day 87, 6 days after developing chest pain, palpitations, and shortness of breath, she was found unresponsive by her husband and pronounced dead in an emergency department. A post-mortem examination concluded that she died from a cardiac dysrhythmia due to eosinophilic myocarditis due to DRESS, with findings of pleural effusions, pericardial effusion, pulmonary edema, cardiomyopathy, and necrotizing myocarditis.

In the second case, a healthy 50-year-old white male who enrolled in a clinical pharmacology study developed an erythematous rash with warmth on day 14. In this study, participants were started on cenobamate 200mg/day and titrated up by 100mg weekly. He was treated with antihistamines and continued in the study until day 22 when he developed facial swelling. He subsequently developed fever (highest reported temperature 103.8°F), swelling of the lips and bilateral eyelids, body aches, and a burning sensation in the areas covered by the rash. He was hospitalized. Lab abnormalities included hyponatremia, elevated creatinine, elevated transaminases and elevated eosinophils. An infectious disease specialist suspected a drug eruption secondary to an antiepileptic drug and a dermatologist felt this was DRESS syndrome. The subject was discharged from the hospital on (b) (6) and labs and symptoms improved. The investigator reported that SAE was resolved on (b) (6).

In the third case, a 36-year-old white female, with complex partial seizure and partial onset seizure with secondary generalization entered a study for cenobamate. Concomitant AED medications included divalproex sodium, levetiracetam, and zonisamide. In this study, subjects began with a cenobamate daily dose of 100 mg, followed by weekly increments of 100 mg in the daily dose, to the target dose (100mg, 200mg, or 400mg). Due to tolerability issues, the dosing was changed in a protocol amendment to initial doses of 50 mg/day and the titration rate was slowed from 100 mg/day/week to 50 mg/day/week until 200 mg/day was reached and then the dose was increased by 100 mg /week in subjects randomized to 400 mg/day. The narrative for this adverse event described confusion about dosing with some sources suggesting missed doses. On study Day 24, she presented to an emergency room with several days of fever and chills; a 2-day history of diffuse macular erythematous and pruritic rash covering the face, trunk, back, arms, and legs; headache; arthralgia; myalgia; and memory problems. Upon admission, she had a temperature of 101.3°F and a morbilliform rash on the abdomen and legs. Laboratory results included elevated transaminases and eosinophils. A dermatology consultant diagnosed DRESS. A chest CT showed mediastinal lymphadenopathy and she was also noted to have bilateral axillary and inguinal lymphadenopathy. Treatment included paracetamol, diphenhydramine hydrochloride, and methylprednisolone which was subsequently switched to prednisone. She was discharged from the hospital and subsequently lost to follow up.

SKLSI and DNP agreed to a study to evaluate whether a lower starting dose and slower cenobamate titration would reduce the risk for DRESS. DNP consulted the Division of Biometrics regarding the planned sample size for this study. SKLSI proposed enrolling 1,000 patients. SKLSI selected this sample size by assuming 0 cases of DRESS would occur with slower titration, allowing SKLSI to cap the DRESS risk at 0.3% (upper bound of 95% CI, given no cases with 1000 exposures). DNP accepted this 0.3% point risk estimate "based on similarity to SJS risk in lamotrigine."² The Division of Biometrics memo included tables of sample size and power calculations for a one arm study but provided the following advice:

The optimal, statistically valid way to compare the two titration schedules would involve a randomized clinical trial in which subjects are randomized to either titration schedule. The comparison of data from a new single arm study to a historic single arm study is limited by the fact that subjects in the new and the historic studies might differ in terms of measured and unmeasured covariates that may be associated with DRESS. Furthermore, even if subjects were comparable at baseline in both studies, the conduct of the two studies and the procedures to collect and record adverse events may differ and may affect the observed rate of DRESS in both studies regardless of treatment effect.

In the conclusion of their memo, the Division of Biometrics wrote the following:

If the review team decides that the main scientific and regulatory comparison of interest is between the new modified titration schedule and the historic study group, and that a single arm study with the new schedule is the only feasible or ethical alternative to compare both treatment arms; then we recommend that the sponsor submit a prospective statistical analysis plan (SAP) to compare the two treatments based on the two studies (new and historic) and that the SAP justify the comparability of the two studies based on the study populations and study procedures.

It does not appear that the Division of Biometrics reviewed a prospective statistical analysis plan for study 021.

021 Trial design

Study YKP3089C021 was an open-label, multicenter (37), multi-country (17) safety study in patients with poorly controlled partial seizures that enrolled 1,339 patients. Enrolled patients received cenobamate 12.5mg/day for 2 weeks, followed by 25mg/day for 2 weeks, followed by upward titration every other week at a rate of 50mg/day to a target dose of 200mg/day. The maximum allowed dose in this study was 400mg/day, and this dose was reached by upward titration every other week at a rate of 50mg/day. After 12 months of participation in the open-label treatment period, subjects were re-evaluated. Those who benefited from treatment with cenobamate were given the option to continue use of the drug at the discretion of the investigator.

Study 021 included elements to protect patients in the event of DRESS and to ensure identification of cases. Below I identify several of these elements. Many of these elements were not present in the

² Memorandum Division of Biometrics 7

earlier studies and as noted above by the Division of Biometrics should be considered when evaluating the lower DRESS risk observed in 021.

021 Study subjects received the following hypersensitivity information on a laminated card to carry with them:

- Rash may occur and may progress to DRESS.
- Rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy, and swelling) may herald a serious medical event and that the subject should report any such occurrence to the investigative site immediately.
- Instructions on whom and where to call in the event a symptom arises and information that can be provided to an emergency room in the event the subject cannot reach the investigator site.
- Reminder to check skin daily for evidence of rash for the first 4 months of therapy.

If a subject reported a rash by telephone, an unscheduled visit was performed promptly. Any subject with a rash or manifestation of hypersensitivity reaction such as lymphadenopathy, fever, or facial swelling was seen immediately at the study site. If it could definitely be determined that the rash or other symptoms were unrelated to study drug, then the subject could be maintained on YKP3809. If the cause of the rash or other symptoms could not be definitely determined immediately, then YKP3089 would have to be discontinued immediately.

The initial physical/rash assessment for hypersensitivity reaction at the investigative site included the following:

- Measurement of body temperature
- Characterization of lymphadenopathy, if present
- Performance of hematology with manual differential and chemistry tests including amylase, lipase, and creatine phosphokinase
- Measurement and description of extent and area of rash
- Evaluation for other causes of multi-organ dysfunction, including antinuclear antibody, blood culture, serology for HIV, hepatitis virus, chlamydia and mycoplasma, Epstein-Barr virus, human herpesvirus 6, and cytomegalovirus, if indicated

If the skin and physical/rash assessment results indicated a rash with the involvement of 1 other organ system or a suspected case of DRESS, the subject was immediately referred to pre-identified local experts and the sponsor was notified immediately.

Investigators were instructed to identify local medical specialists who were able to diagnose and treat suspected DRESS cases. The locally identified specialists were informed by the investigator that their services may be needed during the course of the study. These specialists were identified by the PI prior to any new subjects being initiated at an investigative site. The specialists could have included, but were not limited to, a dermatologist, hepatologist, and/or cardiologist.

During the conduct of the study, a report of subjects with any new hypersensitivity reactions was generated monthly. Hypersensitivity reactions were identified by filtering the existing clinical database for any terms in the standardized MedDRA queries (SMQs) for hypersensitivity and DRESS. All SAEs with similar terms were also identified.

At Visits 1, 14, and yearly thereafter, a full physical exam was performed. At Visits 3 to 10, a limited physical exam to identify evidence of hypersensitivity signs, such as rash, swelling, lymphadenopathy, and fever, was performed.

Site calls to subjects at least once in between the clinic visits to remind them to be vigilant regarding signs and symptoms of DRESS.

In addition to the procedures noted above, compared to trials 013 and 017, study 021 had additional exclusion criteria regarding history of hypersensitivity,

Exclusion criteria related to hypersensitivity 021

1. History of any serious drug-induced hypersensitivity reaction (including but not limited to Stevens Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) or any drug-related rash requiring hospitalization.
2. History of any drug-induced rash or hypersensitivity reaction with documented nature of the rash or hypersensitivity reaction.
3. History of a first-degree relative with a serious cutaneous, drug-induced adverse reaction.

Exclusion criteria related to hypersensitivity 017

19. History of 1 serious drug-induced hypersensitivity reaction (including but not limited to Stevens Johnson syndrome, toxic epidermal necrolysis, DRESS) or any drug-related rash requiring hospitalization.
20. History of AED-associated rash that involved conjunctiva or mucosae or more than 1 maculopapular rash that required discontinuation.

Exclusion criteria related to hypersensitivity 013

- 20) Subject has had greater than 2 allergic reactions to an AED or 1 serious hypersensitivity reaction to an AED.

Study 021 Results

SKSLI reported that no cases of DRESS were identified from trial 021.

DNP Reviewer search for cases of DRESS in trial 021

Using the submitted AE dataset for trial 021, I did not identify any cases that were suggestive of DRESS.

For my first analysis, I reviewed the verbatim AE terms as listed in the dataset and selected any terms suggestive of signs and or symptoms of DRESS, including rashes, allergic reactions, pruritis, fever, lymphadenopathy, hematological abnormalities, liver injury, or kidney injury. I then identified the subjects with at least 2 AE terms from the search (n=35; 27 subjects had at 2 terms, 4 subjects had 3 terms, 3 subjects had 4 terms and 1 subject had 5 terms). From this group, I identified the subjects who had terms suggestive of involvement of more than 1 organ system. For example, one patient had 3 AE

terms identified from the search, but all 3 AE terms were related to liver laboratory results (elevated ALP, elevated ALT, elevated AST) so this patient was dropped from further consideration. This left 12 subjects with AE terms involving one or more organ system. From this group, I excluded patients where the AE terms occurred more than 30 days apart. For example, a patient had an AE of acute kidney injury and another of allergic reaction, but these events occurred more than 1 year apart from each other. After excluding temporally unrelated events, there were 8 patients. None of these 8 patients appeared to have DRESS after further consideration. None of these events were SAEs, none were deemed severe by investigators, and none described involvement of more than 2 organ systems. 6 of the 8 identified patients continued study drug and 2 patients were withdrawn (one for fever and erythematous rash, and one for eosinophils increased and prurigo). 5 of the 8 patients had all AEs classified as resolved or resolving. 3 patients had AEs that were classified as not recovered/not resolved (leukopenia, elevated GGTP, and increased monocytes).

For my second analysis, I used the sponsor created potential DRESS symptom flags in their analysis dataset for 021. In the Phase 2/3 AE dataset (ADAE), SKSLI included the following derived variables: DRESS1 (acute skin rash), DRESS2 (internal organ involvement)³, DRESS3 (enlarged lymph nodes), and DRESS5 (fever above 38 degrees C). I identified patients with at least one of these events. The most commonly reported potential DRESS symptom was internal organ involvement (N=135) followed by acute rash (n=96), fever (n=13), and lymphadenopathy (n=8). 8 patients had 2 potential DRESS symptoms, and none had more than 2 potential DRESS symptoms.

In addition to analyzing the AE data sets, I reviewed the deaths, SAEs and Discontinuations for AEs narratives from study 021 to look for cases of DRESS. None of the 4 deaths appeared to be DRESS cases. I identified 8 rashes that were classified as SAEs and none were suggestive for DRESS cases. Lastly, I reviewed the narratives for potential DRESS symptoms/signs that led to discontinuation and none were suggestive for DRESS.

Comparison of AEs and Discontinuations for AEs

As noted above, study 021 included instructions to investigators and participants about monitoring for DRESS signs and symptoms along with procedures for evaluation and discontinuation that were not part of other development program trials. Given the possibility that these differences could have contributed to the observed reduced risk of DRESS in study 021(ex. by preventing cases through earlier identification and intervention), I examined the risk for skin and hypersensitivity related AEs and discontinuations in trial 021 to look for differences compared to trials 017 and 013. One might expect that the differences in study procedures would have led to increases in identification of AEs such as rashes and to increased discontinuation for these events in study 021. In the following table I provide the percentages of subjects with of Skin/Immune system SOC AEs and discontinuation for such events in trial 021 and trials

³ Included 45 AE terms in the following body systems: Blood and lymphatic system disorders, Gastrointestinal disorders, General disorders and administration site conditions, Hepatobiliary disorders, Immune system disorders, Infections and infestations, Investigations, Musculoskeletal and connective tissue disorders, Nervous system disorders, and Renal and urinary disorders

013 and 017. As displayed below, the percentage of patients with Skin and subcutaneous SOC AEs and discontinuation for such events was higher in trial 021 compared to trials 013 and 017.

Percentages of subjects with of Skin/Immune system AEs and discontinuation for such events and Immune System disorder AEs and discontinuation for such events in trial 021 and trials 013 and 017

Source	Skin and subcutaneous tissue disorders AEs	Skin and subcutaneous tissue D/C for AE	Immune system disorders AEs	Immune system disorders D/C for AE
021	14.3% (191/1339)	3.3% (44/1339)	0.6% (8/1339)	0.1% (1/1339)
DB Pool (017 and 013)	7.0% (31/442)	1.6% (7/442)	0.7% (3/442)	0.5% (2/442)

SOC AE data from ISS Tables 4.1.2; 4.1.4; D/C for SOC AE data from ISS Tables 4.9.2; 4.9.4

After considering the differences in duration of exposure when comparing the double-blind trials 013 and 017 to the open label trial 021, there did not appear to be meaningful differences in risk for Skin and subcutaneous SOC AEs or discontinuation for such AEs. Given the differences in duration for study 021 (1110 subjects exposed for 6 months, study ongoing) compared to trials 013 and 017 (8 weeks, each), any observed differences in risk resulting from the above comparisons could be merely due to longer observation time and greater opportunity to observe an event in study 021. To address this issue, I looked at Skin and subcutaneous SOC AEs and discontinuations for Skin and subcutaneous SOC AEs during the first 8 weeks of study 021 compared to trials 017 and 013. For all Skin and subcutaneous SOC AEs, during the first 8 weeks of trial 021, the risk was 8.8% (118/1339) compared to 7% (31/442) for trials 017 and 013. The rate of discontinuation for these events during the first 8 weeks of study 021 (2.2%, 30/1339) was comparable to the rate in trials 017 and 013 (1.6%, 7/442).

For the 44 subjects who discontinued from 021 for Skin and Subcutaneous tissue AEs, there did not appear to be strong evidence suggesting that these subjects received treatment leading to reduction in DRESS risk (Summaries included as an appendix to this review). Thirty-one individuals had cenobamate discontinued with no other intervention noted and 13 received treatment for their skin AEs (mostly topical corticosteroids and antihistamines). Seven of these treated individuals had diagnoses such as urticaria, angioedema, psoriasis, and eczema and the treatment appeared appropriate. The remaining 6 individuals who received treatment had AEs of rash or pruritis.

Although it is difficult to determine whether monitoring, early discontinuation and treatment prevented any potential cases of DRESS, I identified 2 patients of interest. I provide summaries for those cases below.

YKP3089C021- (b) (6) Approximately 6 weeks after receiving the first dose of cenobamate, the subject experienced mild skin erythema which was 4 cm in diameter on the left neck nape area (visit 6). The study drug was withdrawn. The subject did not experience any lymphadenopathy, temperature

elevation, or facial swelling. The subject's general practitioner made the diagnosis of contact eczema and prescribed a local corticoid and after this the lesions disappeared. The patient had an elevated eosinophil count as noted below.

Test (normal range)	Visit 1 (Screening/B aseline)	Visit 4	Visit 5	Visit 6	Termination visit
Eosinophil Ab (0.0-0.8 x 10 ⁹ /L)	0.1	0.6	0.8	1.0	0.6

YKP3089C021- (b) (6) On study day 4, the subject experienced an SAE of pneumonia and was hospitalized. Treatment while hospitalized included amoxicillin/clavulanic acid. The study drug was not changed due to the event. The subject recovered from the event of pneumonia.

Approximately 3 months after starting cenobamate, the subject experienced mild "prurito with papulas" (papules and pruritus on arms and legs) and abnormal eosinophils lab results. A specialist (not described) diagnosed the event as "unspecified prurigo". Study drug was withdrawn due to the event. Prior to the event, the subject had eosinophil counts ranging from 0.1-0.6 x 10⁹/L (normal range 0.0-0.8 x 10⁹/L). One week before the event, the eosinophils were 1.1 and were 1.2 x 10⁹/L the day after stopping cenobamate. Two weeks after stopping cenobamate, eosinophils were 0.3 x 10⁹/L. ALT, which was normal at baseline increased to 116 U/L the week before the event and was 35 U/L the day after stopping cenobamate. The subject was treated with Fucicort and Clobetasol.

In addition to the discontinuations for Skin and Subcutaneous AEs, I reviewed the hypersensitivity reports that were identified by MedDRA queries during study 021 and submitted to the IND during the study. The sponsor provided 62 reports, 44 of which were the same subjects who discontinued for Skin and Subcutaneous SOC AEs as noted above. The remaining 18 reports included AEs for rash (n=11), itching (n=3), increased eosinophils (n=2), candidiasis, and erythema (n=1, each). None of these 17 reports appeared to describe severe events and many of the narratives documented resolution.

Baseline Demographics

When comparing the populations in the double-blind trials (013, 017), and the Open label study 021, the baseline measured demographics were similar, but there were some differences compared to the Phase I pool. The phase I pool included a higher proportion of males (68%) compared to the double-blind trials (49%) or study 021 (50%). In the Phase I pool 51% of patients were classified as white and 39% black compared to 76% white and 3% black in the double-blind trials and 79% white and 3% black in study 021. Mean and median age and BMI were similar for all three populations (based on data included in ISS tables 21, 22, and 23).

Discussion

Early development program trials demonstrated that cenobamate can cause DRESS at a relatively high rate. A subsequent open label trial that used a lower starting dose and slower titration did not result in any DRESS cases in over 1300 patients. Since the evaluation of DRESS risk with low starting dose/slower

titration was not tested in a randomized controlled trial, the data do not allow for definitive conclusions about whether the revised dosing regimen is solely responsible for the observed reduction in DRESS risk. Other possibilities include differences in underlying studied populations and differences in study conduct (ex. heightened surveillance and early discontinuation). As noted above, there were differences in exclusion criteria in these trials and the Phase 1 pool, from which 2 of the 3 DRESS cases arose, had notable baseline differences in participant race classification. In addition, study 021 included several requirements intended to identify early and protect patients from DRESS. Although these differences did not appear to result in increased reporting or discontinuation Skin or Immune system AEs, the impact of these design differences on observed DRESS risk may not be completely understood.

If cenobamate is approved, the sponsor should accurately describe the risk, monitor for DRESS cases in the post marketing period and search for predictive factors for increased DRESS risk. The sponsor should include standard language about DRESS as a Warning statement in labeling with care to avoid falsely implying that DRESS risk has been eliminated with the use of the lower starting dose/slower titration. The Division should consider requiring a Medication Guide that includes information like that provided to patients in study 021 about signs and symptoms of DRESS and instructions to contact health care providers immediately if these occur. The sponsor should closely monitor for and include as 15-day reports to the Agency any spontaneous reports suggestive of DRESS with the intention of assessing real world use risk and identification of predictive factors. In addition, the sponsor should perform genomic studies to look for predictive factors for DRESS. In previous discussions with the agency, the sponsor admitted that they did not preserve the necessary samples from the development program that would allow such studies, so this should be done in the post marketing period. I do not believe a REMS is required.

Appendix A

Proposed DRESS Diagnostic Criteria

Diagnosis of DRESS is confirmed by the presence of all of the following criteria:

- (1) Cutaneous drug eruption
- (2) Adenopathies ≥ 2 cm in diameter or hepatitis (liver transaminases ≥ 2 times upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis
- (3) Hematologic abnormalities: eosinophilia $\geq 1.5 \times 10^9 L^{-1}$ or atypical lymphocytes

Criteria for potential cases of drug reaction with DRESS by RegiSCAR.

- (1) Hospitalization
- (2) Reaction suspected to be drug-related
- (3) Acute skin rash*
- (4) Fever above $38^{\circ}C$ *
- (5) Enlarged lymph nodes in at least two sites*
- (6) Involvement of at least one internal organ*
- (7) Blood count abnormalities
 - (i) Lymphocytes above or below the laboratory limits*
 - (ii) Eosinophils above the laboratory limits*
 - (iii) Platelets below the laboratory limits*

*Three or more criteria required. RegiSCAR: research group investigating severe cutaneous adverse reactions (SCAR).

Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by a Japanese consensus group.

- (1) Maculopapular rash developing 3 weeks after starting with a limited number of drugs
- (2) Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
- (3) Fever ($\geq 38^{\circ}\text{C}$)
- (4) Liver abnormalities (alanine aminotransferase $\geq 100\text{U}\cdot\text{L}^{-1}$)^a
- (5) Leukocyte abnormalities (at least one present)
 - (a) Leukocytosis ($\geq 11 \times 10^9 \text{L}^{-1}$)
 - (b) Atypical lymphocytosis ($\geq 5\%$)
 - (c) Eosinophilia ($\geq 1.5 \times 10^9 \text{L}^{-1}$)
- (6) Lymphadenopathy
- (7) Human herpesvirus 6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical DIHS) or of the first five (1–5) criteria (atypical DIHS).

^aThis can be replaced by other organ involvement, such as renal involvement.

Appendix B

Examples of DRESS labeling from approved antiepileptic drugs

Tegretol

Has a boxed warning (TEN/SJS, AA) but doesn't include DRESS

Warning Statement

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with Tegretol. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Tegretol should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Depakote

Has a boxed warning (Hepatotoxicity, fetal risk, pancreatitis) but doesn't include DRESS

Warnings and Precautions

5.12 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity Reactions

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has been reported in patients taking valproate. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Valproate should be discontinued and not be resumed if an alternative etiology for the signs or symptoms cannot be established.

Lamictal

Has a boxed warning for serious rashes but doesn't mention DRESS

Warnings and Precautions

5.3 Multiorgan Hypersensitivity Reactions and Organ Failure

Multiorgan hypersensitivity reactions, also known as drug reaction with eosinophilia and systemic symptoms (DRESS), have occurred with LAMICTAL. Some have been fatal or life threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

Fatalities associated with acute multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received LAMICTAL in epilepsy clinical trials. Rare fatalities from multiorgan failure have also been reported in postmarketing use.

Isolated liver failure without rash or involvement of other organs has also been reported with LAMICTAL.

It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with LAMICTAL, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a healthcare provider immediately.

Phenytoin

No boxed warning

Warnings and Precautions

5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, has been reported in patients taking antiepileptic drugs, including DILANTIN. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis

sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. DILANTIN should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Gabapentin

No boxed Warning

Warnings and Precautions

5.1 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has occurred with NEURONTIN. Some of these reactions have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. NEURONTIN should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Appendix C

DRESS Narratives

Study Number: YKP3089C017 Subject ID: (b) (6) MedDRA Preferred Term Drug reaction with eosinophilia and systemic symptoms Relationship to Treatment Probably

Start Date-Stop Date Outcome 09 Mar 2014- Unknown

Subject (b) (6), a 36-year-old white female, with complex partial seizure and partial onset seizure with secondary generalization entered study YKP3089 on (b) (6). She was randomly assigned to YKP3089 200 mg on (b) (6). Concomitant AED medications included divalproex sodium, levetiracetam, and zonisamide. Concomitant non-AED medications included docusate, enoxaparin, gentamycin sulfate, omeprazole, ondansetron, and acetaminophen/chlorpheniramine/phenylephrine. The narrative suggested confusion about dosing. The last dose of the study drug noted in the electronic data capture system was 100 mg on (b) (6). According to the drug accountability record, no study drug was taken from (b) (6) to (b) (6). According to the site, the subject should have been taking 200 mg QD from (b) (6) onward. According to the investigator, the last dose of the study drug, which was 200 mg QD, was taken on (b) (6). During a protocol-specified phone call on (b) (6) the subject complained of tiredness. On (b) (6) (Study Day 24), she presented to an emergency room with several days of fever and chills; a 2-day history of diffuse macular erythematous and pruritic rash covering the majority of body including the face, trunk, back, arms, and legs; headache; arthralgia; myalgia; and memory problems. Upon admission, the subject had a temperature of 101.3°F and a morbilliform rash on the abdomen and legs. Laboratory results are provided in the table below. Chest x-ray and urinalysis were reported as negative (specific results not reported). A lumbar puncture was performed and was reported to be negative, including cultures. A dermatology consultant made the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. A CT scan of the chest and pelvis was performed on (b) (6) to evaluate for lymphoma. Findings included bilateral pleural effusion, right side was greater than the left side, with right lower lobe consolidation. A moderate amount of free fluid in the abdomen and pelvis tracking along the right pericolic gutter was observed, with either a thickened gallbladder wall versus fluid in the gallbladder fossa. Mediastinal lymph nodes were enlarged bilaterally but not consistent with lymphoma along with bilateral axillary and inguinal lymph nodes. Treatment for the event included paracetamol, diphenhydramine hydrochloride, and methylprednisolone which was subsequently switched to prednisone. She also received vancomycin and ceftriaxone; however, antibiotics were stopped as she did not have an acute infectious process. On (b) (6), the subject was discharged from the hospital. According to the investigator, the subject went to an emergency room on (b) (6) and (b) (6) because of rash. Following this, the subject was lost to follow up despite multiple attempts to have her return. The outcome of the event of DRESS syndrome was unknown. The subject did not experience any other AEs at the time of the event of DRESS syndrome. The investigator considered the severe SAE of DRESS syndrome probably related to the study drug. The subject discontinued from the study on (b) (6).
Laboratory results table:

Test Name	(Unit)	Result	Normal Range	Date

Alanine aminotransferase (not reported) 81 Not reported (b) (6)

Aspartate aminotransferase (not reported) 54 Not reported (b) (6)

Eosinophil percentage (%) 13.6 Not reported (b) (6)

Hemoglobin (not reported) 13.3 Not reported (b) (6)

Lymphocyte percentage (%) 16.6 Not reported (b) (6)

Neutrophil percentage (%) 59 Not reported (b) (6)

Platelet count (not reported) 142,000 Not reported (b) (6)

Sodium (not reported) 132 Not reported (b) (6)

White blood cell count (not reported) 4.0 Not reported (b) (6)

White blood cell count (not reported) 3.8 Not reported (b) (6)

Alanine aminotransferase (not reported) 158 Not reported (b) (6)

Alanine aminotransferase (not reported) 117 Not reported (b) (6)

Aspartate aminotransferase (not reported) 158 Not reported (b) (6)

Aspartate aminotransferase (not reported) 117 Not reported (b) (6)

Eosinophil percentage (%) 15.3 Not reported (b) (6)

Hemoglobin (not reported) 10.1 Not reported (b) (6)

Lymphocyte percentage (%) 16.8 Not reported (b) (6)

Neutrophil percentage (%) 64 Not reported (b) (6)

Platelet count (not reported) 169,000 Not reported (b) (6)

White blood cell count (not reported) 5.3 Not reported (b) (6)

White blood cell count (k/mm³) 7.1 Not reported Not reported

Subject 95, a healthy 38-year-old Hispanic female entered the clinical pharmacology QT study YKP3089C020 and had no relevant medical history, no allergies and was taking no medications. On (b) (6) (b) (6) (Day -1) she received a single dose of moxifloxacin-placebo, and was dosed with YKP3089 for 32 days starting on (b) (6) (b) (6) (7 doses of 50 mg YKP3089, 7 doses of 100 mg

YKP3089, 7 doses of 150 mg YKP3089, and 11 doses of 200 mg YKP3089). On (b) (6) (Day 32), the subject called the study nurses to report a mild rash on her face and neck with pruritus. She was advised to hold the dosing on Day 32 but proceeded with the dosing. On the morning of (b) (6) (Day 33), the subject did not dose at home. She returned to the clinic and was noted to have an erythematous macular rash on her face, neck, and upper anterior chest. She denied pruritus, shortness of breath, or edema. Dosing was permanently discontinued at this time. She was given diphenhydramine cream on 1 occasion and several doses of oral diphenhydramine up to 3 times per day. She experienced several mild to moderate AEs in the days and weeks after being discontinued from the study, including depressed mood, face swelling, anxiety, back pain, alopecia, ecchymosis, blurred vision, chest pain, dyspnea, palpitations, headache, cough, fatigue, and asthenia. The depressed mood AE began 7 days after the last dose of study drug and the PI considered it possibly related to study drug. The remaining events began 25 to 50 days after the last dose and the PI considered them all unlikely or unrelated to study drug.

Abnormal laboratory findings at the early termination event on (b) (6) (Day 33) included: alanine aminotransferase (ALT) 107 U/L (reference range: 10 - 60 U/L), aspartate aminotransferase (AST) 64 U/L (reference range: 14 - 47 U/L), basophil percentage 1.5% (reference range: 0 - 0.7%), monocytes 12.4% (reference range: 3.9 - 11.5%), and absolute neutrophils 1.8 thou/ μ L (reference range 1.9 - 7.9 thou/ μ L). Vital signs and ECG parameters were within normal limits at the early termination event. The subject was instructed to return to the clinic for follow-up laboratory testing in 1 to 3 days. Refer to Table 1, Table 2 , and Table 3 for notable liver enzymes and white blood cell (WBC) differential parameters.

Table 1: Notable Liver Enzymes for Subject (b) (6) (Study YKP3089C020)

Study Day	Date (b) (6)	ALT (10-60 U/L)	AST (14-47 U/L)	ALP (41-129 U/L)	Total Bilirubin (0.2-1.6 mg/dL)	Direct Bilirubin (0-0.2 mg/dL)	GGT (6-74 U/L)	LDH (125-248 U/L)
Screen		18	23	48	0.2	0.2	—	—
Day -3		15	22	49	0.2	0.2	—	—
Day 33*		107	64	72	0.2	0.2	—	—
Day 39		238	187	—	—	—	—	—
Day 39#		296	227	—	—	—	—	—
Day 40		456	376	113	0.4	0.2	214	556
Day 41		616	414	171	0.8	0.6	362	619
Day 42		733	432	218	1.5	1.3	408	750
Day 44		937	610	214	2.3	2.0	345	872
Day 44#		1093	657	211	2.6	—	—	—
Day 45#		1091	775	202	2.7	2.4	—	—
Day 46#		1327	865	207	2.9	—	—	—

Day 49	(b) (6)	997	358	215	1.6	0.9	292	536
Day 52		1000	575	200	1.1	0.6	261	581
Day 57		298	56	139	—	0.4	185	254
Day 64		74	27	89	—	0.2	111	237
Day 71		107	43	80	0.4	0.2	95	314
Day 78		62	—	—	—	—	66	269
Day 83		43	43	—	—	—	—	—
*ET (early termination)								
#Laboratory results from hospital records; reference ranges are approximate.								
Bolded values are abnormal (out-of-range).								

Table 2: Notable WBC Differential Parameters for Subject (b) (6) - Part 1

Study Day	Date	WBC (3.9-10.7 thou/μL)	Basophils (0-0.7%)	Absolute Basophils (0-0.1 thou/μL)	Eosinophils (0.2-9%)	Absolute Eosinophils (0-0.8)	Lymphocytes (14-43%)
Screen	(b) (6)	4.6	0.7	0.0	1.8	0.1	36.0
Day -3		5.4	0.6	0.0	2.4	0.1	40.4
Day 33*		4.0	1.5	0.1	7.6	0.3	34.3

Study Day	Date (b) (6)	WBC (3.9-10.7 thou/ μ L)	Basophils (0-0.7%)	Absolute Basophils (0-0.1 thou/ μ L)	Eosinophils (0.2-9%)	Absolute Eosinophils (0-0.8)	Lymphocytes (14-43%)
Day 39	(b) (6)	—	—	—	—	—	—
Day 39#		—	—	—	8	—	—
Day 40		11.3	2.9	0.3	7.9	0.9	32.6
Day 41		12.4	4.4	0.5	6.7	0.8	35.0
Day 42		13.7	2.9	0.4	7.1	1.0	42.2
Day 44		16.2	0.0	0.0	3.0	0.5	35.0
Day 44#		16.3	1.0	—	5.0	—	54.0
Day 45#		15.4	0.0	—	12.0	—	41.0
Day 46#		16.2	—	—	—	—	—
Day 49		17.2	1.0	0.2	26.0	4.5	30.0
Day 52		10.4	1.9	0.2	31.5	3.3	31.5
Day 57		10.7	0.7	0.1	8.0	0.9	49.5
Day 64		—	—	—	—	—	—
Day 71		10.3	0.4	0.0	15.5	1.6	20.2
Day 78		13.2	0.7	0.1	11.2	1.5	22.7
Day 83		11.3	0.4	0.0	13.7	1.6	34.5

*ET (early termination)

#Laboratory results from hospital records; reference ranges are approximate. Bolded values are abnormal (out-of-range).

Table 3: Notable WBC Differential Parameters for Subject (b) (6) - Part 2 (Study YKP3089C020)

Study Day	Date (b) (6)	Absolute Lymphocytes (1-3 thou/ μ L)	Monocytes (3.9-11.5%)	Absolute Monocytes (0.2-0.8 thou/ μ L)	Neutrophils (42-80%)	Absolute Neutrophils (1.9-7.9 thou/ μ L)
Screen	(b) (6)	1.6	8.1	0.4	53.4	2.4
Day -3		2.2	6.4	0.4	50.2	2.7
Day 33*		1.4	12.4	0.5	44.2	1.8
Day 39		—	—	—	—	—
Day 39#		—	—	—	43	—
Day 40		3.7	10.5	1.2	46.1	5.2
Day 41		4.3	10.1	1.3	43.8	5.4

Study Day	Date (b) (6)	Absolute Lymphocytes (1-3 thou/ μ L)	Monocytes (3.9-11.5%)	Absolute Monocytes (0.2-0.8 thou/ μ L)	Neutrophils (42-80%)	Absolute Neutrophils (1.9-7.9 thou/ μ L)
Day 42	(b) (6)	5.8	12.8	1.8	35.0	4.8
Day 44		5.6	9.0	1.5	53.0	8.6
Day 44 [#]		—	3.0	—	37.0	6.03
Day 45 [#]		—	1.0	—	41.0	7.08
Day 46 [#]		—	—	—	—	—
Day 49		5.2	5.0	0.9	38.0	6.5
Day 52		3.3	9.5	1.0	25.6	2.7
Day 57		5.3	6.4	0.7	35.4	3.8
Day 64		—	—	—	—	—
Day 71		2.1	3.6	0.4	60.3	6.2
Day 78		3.0	6.1	0.8	59.3	7.8
Day 83		3.9	9.2	1.0	42.2	4.8

*ET (early termination)

[#]Laboratory results from hospital records; reference ranges are approximate. Bolded values are abnormal (out-of-range).

The next morning (b) (6) [Day 34] she reported by telephone that the rash on her chest was improving, as was the pruritus of her neck. On (b) (6) (Day 39), the subject returned to the clinic and the rash was noted to be worse; a generalized maculopapular rash was now covering her face, neck, and trunk, front and back down to her buttocks. The subject complained of pruritus and stated that the diphenhydramine was not helping. In addition, she reported difficulty breathing, and said she felt the need to cough to breathe better. She also reported flank pain and nausea. Upon examination, lung sounds were clear, but diminished. Vital signs showed blood pressure of 101/65 mmHg, pulse rate of 98 bpm, respirations of 18 rpm, temperature of 99.8°F, and oxygen saturation 96% on room air. The subject's ALT (238 U/L) and AST (187 U/L) were noted to be significantly increased from the early termination visit 6 days prior as shown in Table 1. Due to her worsening symptoms, the subject was referred to a local emergency department. At the emergency room she described of acute non-radiating back pain (right mid and right low back). She was alert and oriented and vital signs included blood pressures ranging from 91/58 to 98/62 mmHg, pulse rates of 93 to 104 bpm, temperature of 100.0°F, and oxygen saturation percentages of 96% to 98% on room air. A computed tomographic (CT) scan of the abdomen and pelvis was performed and showed a non-obstructing stone in the area of the right kidney and a complex ovarian cyst, with recommendation for a pelvic ultrasound. The subject was given intravenous normal saline 1000 mL, Solu-Medrol® 125 mg, and Benadryl® 25 mg. She was discharged with diagnoses of drug rash, ureterolithiasis - renal colic, and ovarian cyst. She was sent with prescriptions for ibuprofen, Norco, Zofran®, and prednisone 20 mg (with taper instructions), and was instructed to follow-up with her private physician in 2 to 3 days.

She returned to the clinic for follow-up visits on (b) (6) (Day 40) and (b) (6) (Day 41) and reported no improvement to the rash or pruritus, and continued nausea. At both visits, her ALT and AST continued to increase, along with several other serum liver function tests (alkaline phosphatase [ALP], direct bilirubin, gamma-glutamyl transferase (GGT), and lactate dehydrogenase [LDH]). Additionally, several WBC differential parameters were out of range as shown in Table 1, Table 2, and Table 3. Vital signs showed blood pressures ranging from 92/62 to 107/69 mmHg, pulse rates of 82 to 123 bpm, respirations of 20 rpm, and temperatures of 97 to 100°F.

On (b) (6) (Day 42), she returned to the clinic for follow-up laboratory work. The erythematous macular rash was still present on her chest, abdomen, back, and legs and she continued to have nausea. She was then taken to a scheduled dermatology appointment. Her rash was noted to be located throughout her body, and was itchy and red. She stated she felt better after the prednisone, but the improvement did not last all day. A punch biopsy result was consistent with DRESS syndrome. Viral laboratory panel test results showed: Epstein-Barr virus (EBV) antibody panel presence of Immunoglobulin G (IgG) antibodies (1.46; reference range: 0 - 0.9], but no Immunoglobulin M (IgM) antibodies (0.00 reference range: 0 - 0.9); Herpes virus-6 deoxyribonucleic acid (DNA) negative (0; reference range: 0 - 500 copies/mL) and herpes virus-6 IgG antibodies detected (1:20; reference range < 1:10); Cytomegalovirus (CMV) antibody panel presence of IgG antibodies (2.29; reference range: 0 - 0.9) but no IgM antibodies (0.00; reference range: 0 - 0.8). Additionally, an aldolase value was elevated at 28.0 U/L (local laboratory reference range: 1.2 - 7.6 U/L). She was prescribed triamcinolone cream for the rash, the prednisone dosage was set at 20 mg, and additionally she was placed on calcium and vitamin D for bone health prophylaxis while taking the prednisone.

On (b) (6) (Day 43) she reported by telephone no improvement in her AEs and was instructed to return for a laboratory recheck and was advised to call the clinic or go to an emergency room if symptoms worsened. She returned to the clinic on (b) (6) (Day 44) and her rash was noticeably worse; also pronounced diffuse adenopathy was noted. She denied nausea, vomiting, and diarrhea, but generally felt ill. Her ALT (937 I/U) and AST (610 I/U) were continuing to increase. Coagulation parameters were obtained and showed an elevated prothrombin time (PT, 13.5 seconds; reference range: 9.6 - 11.6 seconds) and international normalized ratio (INR, 1.3; reference range: 0.9 - 1.1), and a partial thromboplastin time (PTT) within normal range (26 seconds; reference range: 23 - 32 seconds). Her blood pressure was 106/69 mmHg, pulse rate 96 bpm, respirations 20 rpm, and temperature 99.8°F. Due to her worsening rash and elevated transaminases on (b) (6) (Day 44), she was instructed to go to the emergency room, and was subsequently admitted to the hospital for management of the DRESS syndrome. She was followed by an internal medicine doctor and a hepatologist. She continued receiving prednisone 60 mg and triamcinolone cream along with heparin 5000 units subcutaneous, hydroxyzine 25 mg, hydrocortisone cream, and diphenhydramine cream. She had a liver duplex ultrasound that was normal. Vital signs included blood pressures of 85 - 105/58 - 75 mmHg, pulse rates of 70s to 90s bpm, respiratory rate of 16 rpm, temperatures ranging from 36.7 to 38.1°C, and oxygen saturation of 94% on room air. Her ALT and AST increased further while hospitalized, with maximum ALT of 1327 U/L and AST of 865 U/L on (b) (6) (Day 46). In addition to the elevated transaminases and out-of-range blood count differential parameters during the hospitalization, the subject's hemoglobin and hematocrit

values were low, with hemoglobin values ranging from 10.9 to 11.8 g/dL (hospital reference range: 12.0 - 15.5 g/dL) and hematocrit values ranging from 32.7% to 34.7% (hospital reference range: 34.9% - 44.5%). Her PT remained elevated while hospitalized on (b) (6) (Day 45) and (b) (6) with values of 15.4 and 16.4 seconds, respectively (hospital reference range: 11.8 - 14.2 seconds). The corresponding INR values were 1.24 and 1.34.

She was discharged to home on (b) (6) (Day 46), with prescriptions for prednisone 60 mg with taper over the next 2 weeks, hydroxyzine 25 mg, triamcinolone cream, and diphenhydramine cream. On (b) (6) (Day 49), she returned to the clinic and her ALT (997 IU) and AST (1327 IU) remained elevated but were trending downward. She reported that the pruritus to the rash was still present. Follow-up coagulation studies were within normal range on (b) (6) (Day 49) and (b) (6) (Day 52).

On (b) (6) (Day 50), the subject was seen at a hepatologist's office. Her rash was drastically improved, and all vital signs were all within normal range. Her liver enzymes were improving. It was recommended that she continue to be followed by her primary doctor and to have her liver enzymes checked every week until they normalized. Her medications included prednisone 20 mg with taper over the next 2 weeks, hydroxyzine 25 mg, triamcinolone cream, and diphenhydramine cream.

On (b) (6) (Day 52), she returned to the clinic and lymphadenopathy was still present, most notably along the right posterior cervical area. She felt that the swelling was improving. Lung sounds were improved and there were no signs of respiratory distress. ALT (1000 I/U) and AST (575 I/U) remained elevated, eosinophil percentage peaked (31.5%), and neutrophil percentage (25.6%) was at its low point at that time. On (b) (6) (Day 57), the subject returned to the clinic and her ALT (198 I/U) and AST (56 I/U) were still elevated but improved. On (b) (6) (Day 58), she was contacted by phone regarding out-of-range laboratory results; the subject stated she would return in 1 week. Over the next few weeks (b) (6) [Day 64] through (b) (6) [Day 83], she returned to the Celerion clinic and/or spoke with clinic staff over the phone every day. Her ALT and AST were trending down towards normal range; as were the other liver function tests. Most blood count differential parameters began to improve at subsequent rechecks. On (b) (6) (Day 64), she returned to the clinic and reported the rash was improved but noted that sometimes it returned then went away. She also reported that since (b) (6) (Day 57), she noticed facial swelling in the middle of her face and lips, which was worse upon waking in the morning. It had been progressively getting more noticeable and she reported that now the inside of her mouth was swollen. She denied shortness of breath or difficulty breathing. Upon examination, her face and oral mucosa were noticeably swollen, and her swollen posterior cervical lymph node remained enlarged.

On (b) (6) (Day 65), she reported by phone that the rash was more noticeable and red, and her facial edema was about the same. She also stated that it was her last day of prednisone dosing. On (b) (6) (Day 66), she reported by phone that facial swelling was the same, the pruritus continued, and that the diphenhydramine was not helping. She was advised to restart the hydroxyzine and triamcinolone, or hydrocortisone creams as needed. On (b) (6) (Day 67), she reported by phone

and her facial swelling had increased. She denied breathing, and stated that the hydroxyzine triamcinolone cream seemed to be helping the pruritus. On [REDACTED] (b) (6) (Day 68), she returned to the clinic and had facial swelling, and a generalized maculopapular rash involving the trunk, neck, bilateral arms, and upper legs. She was started on a new course of prednisone. The subject reported feeling sad.

On [REDACTED] (b) (6) (Day 69), she reported by phone and reported that her facial swelling was decreased by 50%. On [REDACTED] (b) (6) (Day 70), she reported by phone that her facial edema continued to improve, but that she still had the rash with pruritus. She again reported feeling sad due to being homebound, and concern over finances. On [REDACTED] (b) (6) (Day 71), the subject returned to the clinic and her facial edema was continuing to improve. On [REDACTED] (b) (6) (Day 72), she reported by phone that the rash, facial swelling, pruritus, and feeling sad continued with no improvement. On [REDACTED] (b) (6) (Day 73), reported by phone that the rash was improving, and that the facial swelling was still present and that her eyes are now swollen despite the concomitant medications. On [REDACTED] (b) (6) (Day 74), her condition was unchanged but on [REDACTED] (b) (6) (Day 75), she felt better and had started to see improvement on her face and on [REDACTED] (b) (6) (Day 76), she stated that the facial edema and rash were now minimal, and that she was feeling less sad.

On [REDACTED] (b) (6) (Day 77), she reported lower back pain and small bruises on her right leg, but she stated the rash, facial edema, and feeling sad were minimal. On [REDACTED] (b) (6) (Day 78), she returned to the clinic and stated she was feeling much better and the AE of feeling sad was improved but she reported ecchymosis to her left leg and hair loss. She was still taking prednisone. On [REDACTED] (b) (6) (Day 79), she reported by phone that all AEs were improving. On [REDACTED] (b) (6) (Day 80), she reported by phone that she still had facial edema and was having feelings of sadness and she was concerned about losing so much hair. She stated she took her last dose of prednisone.

On [REDACTED] (b) (6) (Day 81), she reported by phone that she was having chest pain that started the previous day. She returned to the clinic, and stated that her chest pain radiated to her back, and was accompanied by shortness of breath, palpitations, and blurred vision. She stated she was going to an emergency room after the clinic visit but her chest pain improved so she did not go. The clinic staff advised the subject to go to the emergency room, but she stated she would go if the chest pain worsened but she did not want to go at that time.

On [REDACTED] (b) (6) (Day 82), she reported by phone that her chest pain improved and that her shortness of breath, palpitations, and blurred vision were resolved. Her facial edema was almost gone, the ecchymosis to her leg was improving, and the hair loss continued.

On [REDACTED] (b) (6) (Day 83), she returned to the clinic and her physical examination was much improved. She had mild edema to her cheeks and periorbital areas, and minimal rash to her bilateral forearms. She stated that she had increased stressors in her home life and finances over the past few days. Her chest pain was better at the time of the visit, but she still noted some intermittent chest pain with exertion and she reported a recent onset of fatigue. Vital signs included a blood pressure of 94/65

mmHg and pulse rate of 83 bpm. An ECG was within normal range, including a QTcF interval of 397 msec. Her liver enzymes were within normal range (ALT 43 I/U and AST 43 I/U), however, several WBC differential parameters were still elevated, including a WBC count of 11.3 thou/ μ L and eosinophil percentage of 13.7%.

On [REDACTED] (b) (6) (Day 86), she reported by phone ongoing chest pain, worse with movement. She denied shortness of breath but did state her chest hurt when she took a deep breath. She also reported ongoing stress with regard to family finances and the need to find childcare for her return visits. She was reminded to go the emergency room for chest pain. The clinic staff also suggested relaxation techniques, such as taking a warm bath or listening to music. Later that evening she complained of chest pain to her husband, but it subsided.

On [REDACTED] (b) (6) (Day 87), she was found unresponsive by her husband and emergency medical services transported her to a local emergency room where she was pronounced dead. On 12 August 2015, a post-mortem examination concluded that she died from a cardiac dysrhythmia due to eosinophilic myocarditis due to DRESS, with findings of pleural effusions, pericardial effusion, pulmonary edema, cardiomyopathy, and necrotizing myocarditis.

Subject [REDACTED] (b) (6) a healthy 50-year-old Caucasian male enrolled in a Phase 1, single-center, randomized, double-blind, placebo-controlled, multiple ascending dose study. He had no relevant medical history or reported medications. On Day 14 [REDACTED] (b) (6), approximately 5.4 hours after receiving the 4th dose of 400 mg YKP3089, he experienced warmth to the trunk and developed a diffuse erythematous rash to the trunk, arms, and legs (bilaterally). He was treated with oral diphenhydramine hydrochloride that day. The PI examined him the following morning and found a diffuse erythematous rash to trunk, arms and legs that was very red and pruritic. The subject denied any difficulty swallowing or breathing and dosing was continued. That evening he again received oral diphenhydramine for complaint of pruritus. Later that evening, he also complained of feeling weak. Over the next 6 days the rash showed little improvement and he complained of continued itching, which was treated with oral diphenhydramine 50 mg. On Study Day 22 [REDACTED] (b) (6) the rash was noted to include the palms of the hand and soles of the feet. No stridor was noted, and there was no uvular or tongue swelling; the subject denied difficulty swallowing and was allowed to dose. Later that same day, the subject was noted to have soft facial tissue swelling as well as swelling of the digits bilaterally. No swelling of the lips or oral mucosa was noted. The PI discontinued dosing and kept the subject domiciled in the clinic for safety. The subject received a total of 5 doses each of 200, 300, and 400 mg YKP3089 and 7 doses of 500 mg YKP3089 before the study drug was discontinued on Day 22. On Day 23 [REDACTED] (b) (6) in the morning, the subject had increased weakness; stating that it was difficult to get out of bed. The rash persisted, and the subject denied difficulty breathing or swallowing. That afternoon, he began to have swelling of the lips and bilateral eyelids, body aches, and a burning sensation in the areas covered by the rash. He received oral diphenhydramine, oral paracetamol, and topical hydrocortisone. Vital signs were normal with the exception of a pulse rate of 99 bpm at a single time point. That evening, his temperature increased to 103.8°F, accompanied by a pulse rate of 106 bpm. He was given paracetamol.

On Day 24 (b) (6) he had a temperature of 103.2°F, and increased heart rate of 106 bpm. He received oral diphenhydramine and paracetamol. The pruritic rash was still present. He had continued weakness with observed difficulty changing positions in bed. He reported feeling achy all over, with moderate pain to entire body. He also was noted to have generalized pustules over his face and increased swelling to the facial soft tissues. He was given intramuscular methylprednisolone sodium succinate.

Laboratory results included the following: sodium 122 mEq/L (reference range 133 - 145 mEq/L), chloride 88 mEq/L (reference range: 97 - 105 mEq/L), blood urea nitrogen (BUN) 28 mg/dL (reference range: 6 - 20 mg/dL), creatinine 1.70 mg/dL (reference range: 0.8 - 1.3 mg/dL), bicarbonate 21 mmol/L (reference range 24.2 - 33.6 mmol/L), ALT 517 U/L (reference range 11 - 65 U/L), aspartate aminotransferase (AST) 173 U/L (reference range: 15 - 46 U/L), GGT 255 U/L (reference range 7 - 62 U/L), white blood cells (WBCs) 13.8 Thou/ μ L (reference range: 3.4 - 10.5 Thou/ μ L), lymphocytes 8.6% (reference range: 16.8 - 51.7%), neutrophils 84.0% (reference range: 40.2 - 75.0%), and absolute neutrophil count (ANC) 11.6 Thou/uL (reference range: 1.5 - 7.0 Thou/L). Glomerular filtration rate (GFR), while still within normal limits at 66 mL/min (reference range: > 60 mL/min), was significantly lower than at baseline (125 mL/min). The decision was made to transfer the subject via ambulance to the local emergency room.

At the hospital, initial blood work was consistent with the findings at the site listed above. The ER also reported the following: albumin 2.5 g/dL, calcium, 7.8 mg/dL, and INR 1.41. In addition, 2 blood cultures revealed *S. Epidermidis*. Treatment with Vancomycin 1 g QD was initiated along with normal saline, heparin, and Solu-Medrol® 120 mg /day.

An infectious disease physician felt the culture results represented contaminant based on the lack of corroborating symptoms and discontinued the Vancomycin. The infectious disease physician believed the diffuse maculopapular rash was likely a drug eruption secondary to an antiepileptic drug. Within 24 hours, the patient showed signs of clinical improvement with less fever, feeling stronger and some resolution of the rash. Renal function improved, WBC counts reduced with normalization of granulocytes and calcium increased. Hepatitis panel for A, B and C was negative. However, on (b) (6) (b) (6) AST increased to 568 U/L, ALT increased to 809 U/L and alkaline phosphatase increased to 133 U/L. On (b) (6) a dermatologist reported a diffuse dusky discoloration of skin involving hands and feet plus areas of fine scaling and palpable purpura extensive on legs. His first impression was drug hypersensitivity syndrome including systemic symptoms and leukocytoclastic vasculitis. A CBC with differential ordered by the dermatologist revealed eosinophils of 11% with a total WBC of 7.1 Thou/ μ L. Based on the elevated eosinophil count, the dermatologist believes the condition of the subject can best be characterized as a DRESS syndrome. By (b) (6) the rash was resolving and the liver and kidney functions tests were returning towards normal. By discharge from the hospital, the sodium, chloride, BUN, creatinine, bicarbonate, and WBC count were within normal limits. The ALT and AST were still elevated but trending downwards. Hemoglobin level was still low at 11.5 g/dL (reference range 12.6 - 16.8 g/dL) as was albumin at 2.7 g/dL (reference range 4 - 5.2 g/dL). The subject was alert and oriented, in stable condition, and his symptoms had significantly improved. The subject was discharged from the hospital on (b) (6) and returned to the clinical site. The subject continued to follow

up with the clinic until resolution of his symptoms. Labs drawn on (b) (6) showed that the international normalized ratio (INR), which was elevated during hospitalization to 1.41 (reference range: 0.9 - 1.1) and AST were now within normal limits and the GFR had improved back to baseline at 113 mL/min. Safety labs drawn on (b) (6) showed that hemoglobin and albumin were within normal limits and that GGT and ALT were only slightly elevated. The symptoms of itching and rash continued to improve per follow-up phone calls by the subject. The SAE was considered resolved on (b) (6)

(b) (6)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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09/12/2019 09:21:13 AM

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