CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212839Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 20, 2019
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablet, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	SK Life Science, Inc.
OSE RCM #:	2018-2559-5
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 20, 2019 for Xcopri. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Xcopri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and label and labeling memorandums. [abcde]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Rider B. Label and Labeling Review for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 APR 18. RCM No.: 2018-2559.
[b] Little C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 AUG 08. RCM No.: 2018-2559-1.
[c] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 SEP 23. RCM No.: 2018-2559-2.
[d] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 OCT 31. RCM No.: 2018-2559-3.
[e] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 NOV 15. RCM No.: 2018-2559-4.

6 Pages of Draft Labeling have been Withheld in Full as b4(CCI/TS) immediately following this page

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/s/

BRIANA B RIDER on behalf of CELESTE A KARPOW
11/21/2019 10:24:46 AM

BRIANA B RIDER
11/21/2019 10:25:07 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency

Date:	November 18, 2019
Reviewer:	Silvia Perez-Vilar, PharmD, PhD Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	(b) (4) (cenobamate, YKP3089)
Application Type/Number:	NDA 212839
Applicant/sponsor:	SK Life Science, Inc.
OSE RCM #:	2019-2159

1. BACKGROUND INFORMATION

1.1. Medical Product

Cenobamate[1] ([(b) (4)] SK Life Science, Inc.) is a novel tetrazole derived compound with one chiral center. The proposed indication is treatment of partial-onset seizures in adult patients. 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. Cenobamate is administered orally. The proposed dosing 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; the dose may be increased 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. Cenobamate is mainly confined to plasma and extensively metabolized in the 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. No major circulating metabolites (i.e., >10% of total drug-related material) have been identified in human plasma. Following single oral doses of 100– 400 mg, it has a mean elimination half-life of 50–60 hours.[2] Cenobamate inhibits CYP2B6, CYP2C19, and CYP3A, but it does not inhibit CYP1A2, CYP2C8, CYP2C9, or CYP2D6; it induces CYP2B6, CYP2C8, and CYP3A4, but it does not induce CYP1A2, CYP2C9, or CYP2C19.[3]

The New Drug Application (NDA) submission included two adequate and well-controlled double-blind, randomized, placebo-controlled, parallel group multicenter, multinational clinical trials.[4,5] A third multinational clinical trial, a safety and open label study to assess the safety and pharmacokinetics of YKP3089 as adjunctive therapy in subjects with partial onset seizures[6] was also submitted to support safety. Several phase I studies[7] were also reviewed for safety

[1] Cenobamate drug substance was originally given a laboratory code, YKP3089. The name cenobamate was adopted as an International Nonproprietary Name (INN) and both terms are used interchangeably throughout the New Drug Application (NDA)
[2] Draft clinical review dated October 15, 2019
[3] Proposed [(b) (4)] labeling dated November 4, 2019
[4] NCT number: 01397968. *"A Phase 2 Multicenter, Double-blind, Randomized, Adjunctive, Placebo-controlled Trial With an Open-label Extension to Evaluate the Efficacy and Safety of YKP3089 in Subjects With Treatment Resistant Partial Onset Seizures."* Accessed on October 16, 2019 at https://clinicaltrials.gov/ct2/show/NCT01397968?term=01397968&rank=1)
[5] NCT number 01866111. *"A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of YKP3089 as Adjunctive Therapy in Subjects With Partial Onset Seizures, With Optional Open-Label Extension."* Accessed on October 16, 2019 at https://clinicaltrials.gov/ct2/show/NCT01866111?term=01866111&rank=1)
[6] NCT number: 02535091. *"An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089 as Adjunctive Therapy in Subjects With Partial Onset Seizures."* Accessed on October 16, 2019 at https://clinicaltrials.gov/ct2/show/NCT02535091?term=02535091&rank=1)
[7] Studies AA22780, AA24143, AA39450, AA40616, AA41857, C009–C011, C014, C016, C018–C020, C022, C024, C026–C030

purposes.[8] The proposed label (as of November 4, 2019) includes warnings and precautions for drug reaction with eosinophilia and systemic symptoms (DRESS)/multi-organ hypersensitivity, QT shortening, suicidal behavior and ideation, neurological adverse reactions, and XCOPRI withdrawal.

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects in clinically recognized pregnancies is 2–4% (Centers for Disease and Prevention 2008, U.S. Food and Drug Administration 2014). Epilepsy is a common neurological condition in women globally, with an estimated lifetime prevalence of 7.6 cases per 1,000 women (Fiest, Sauro et al. 2017). The condition presents unique management challenges in women because hormonal changes throughout a woman's life can affect seizure control, antiepileptic drug metabolism, and vice versa (Stephen, Harden et al. 2019). Because cenobamate inhibits CYP3A, which is involved in metabolism of oral contraceptives, concomitant use of cenobamate may reduce the effectiveness of hormonal oral contraceptives.[9] In pregnant women, epilepsy is associated with a small, but significant, increase in adverse pregnancy outcomes such as antepartum and post-partum hemorrhage, spontaneous abortion, hypertensive disorders, induction of labor, cesarean section, preterm birth, and fetal growth restriction (Viale, Allotey et al. 2015).

Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of cenobamate. Female subjects who were pregnant or lactating were excluded from enrolling in the cenobamate clinical studies. Despite requirements for contraception, a total of ten cenobamate-treated subjects reported pregnancies across the clinical development program: there were three elective terminations (reason not reported), two live births (both were cesarean sections at 38 weeks of gestation; no congenital malformations or other adverse birth outcomes reported), two spontaneous abortions (at ≤six weeks and two weeks and six days of gestation, respectively), two unknown pregnancy outcomes, and one ectopic pregnancy.[10] In animal studies, administration of cenobamate during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (increased embryofetal mortality, decreased fetal and offspring body weights, offspring neurobehavioral and reproductive impairment) at clinically relevant drug exposures. Teratogenic potential could not be fully evaluated because of the high rate of embryofetal deaths, which resulted in an inadequate number of fetuses examined. [11,12]
The Division of Neurology Products (DNP) did not feel that there was sufficient data, including animal data, at the time of NDA review to determine whether there is a known serious risk or a signal of serious risk in humans. Consistent with DNP practice over the years, DNP determined that these results are most consistent with a PMR that seeks to identify an unexpected serious risk when available data indicate potential for serious risk.

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[8] Draft Clinical Review dated October 15, 2019
[9] Proposed (b) (4) labeling dated November 4, 2019
[10] Integrated Summary of Safety Cenobamate (YKP3089). SK Life Science, Inc.
[11] Proposed (b) (4) labeling dated November 4, 2019
[12] The applicant will be required to conduct an embryofetal development study in rats to further examine the potential for malformations.

In the current proposed labeling, as of November 4, 2019, the Risk Summary in Section 8.1 Pregnancy states:

"***Pregnancy exposure registry.*** *There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as XCOPRI, during pregnancy. Encourage women who are taking XCOPRI during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll-free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.*

Risk Summary. *There are no adequate data on the developmental risk associated with the use of XCOPRI in pregnant women. In animal studies, administration of cenobamate during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (increased embryofetal mortality, decreased fetal and offspring body weights, neurobehavioral and reproductive impairment in offspring) at clinically relevant drug exposures [see Data].*

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data. Animal Data*. Oral administration of cenobamate (0, 10, 30, or 60 mg/kg/day) to pregnant rats during the period of organogenesis resulted in increased embryofetal mortality, reduced fetal body weights, and incomplete fetal skeletal ossification at the highest dose tested, which was associated with maternal toxicity. There was a small increase in visceral malformations at the high dose; however, teratogenic potential could not be fully evaluated because of the high rate of embryofetal deaths, which resulted in an inadequate number of fetuses examined. Maternal plasma exposure (AUC) at the no-effect dose for adverse effects on embryofetal development (30 mg/kg/day) was less than that in humans at the maximum recommended human dose (MRHD) of 400 mg. Oral administration of cenobamate (0, 4, 12, or 36 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality at the highest dose tested, which was associated with maternal toxicity. Maternal plasma exposure at the no-effect dose (12 mg/kg/day) for adverse effects on embryofetal development was less than that in humans at the MRHD. When cenobamate (0, 11, 22, or 44 mg/kg/day) was orally administered to female rats throughout pregnancy and lactation, neurobehavioral impairment (learning and memory deficit and increased auditory startle response) was observed in the offspring at all doses and decreased preweaning body weight gain and adverse effects on reproductive function (decreased numbers of corpora lutea, implantations, and live fetuses) were seen in the offspring at the high dose. Maternal plasma exposure at the lowest effect dose ((b)(4) mg/kg/day) for adverse effects on pre- and postnatal development was less than that in humans at the MRHD."*

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☒ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study. A PMR for a pregnancy registry will not be issued. There is an existing pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs, such as XCOPRI, during pregnancy, the North American Antiepileptic Drug (NAAED) Pregnancy Registry (http://www.aedpregnancyregistry.org/), in which the sponsor is expected to enroll.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☐ Outcomes

☐ Covariates

☒ Analytical Tools

For any checked boxes above, please describe briefly:

Analytical tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

Because broad-based signal detection is not currently available, other parameters have not been assessed.

2.5. Please include the proposed PMR language in the approval letter.

The following language has been proposed by the Division of Neurology Products (DNP) as of October 23, 2019 for the PMR related to pregnancy outcomes:

"Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Xcopri (cenobamate) during pregnancy compared to an unexposed control population."

REFERENCES

Centers for Disease, C. and Prevention (2008). "Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005." MMWR Morb Mortal Wkly Rep **57**(1): 1-5.
Fiest, K. M., K. M. Sauro, S. Wiebe, S. B. Patten, C. S. Kwon, J. Dykeman, T. Pringsheim, D. L. Lorenzetti and N. Jette (2017). "Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies." Neurology **88**(3): 296-303.
Stephen, L. J., C. Harden, T. Tomson and M. J. Brodie (2019). "Management of epilepsy in women." Lancet Neurol **18**(5): 481-491.
U.S. Food and Drug Administration. (2014). "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format. Draft Guidance." Guidance for Industry Retrieved October 18, 2019, from https://www.fda.gov/media/90160/download.
Viale, L., J. Allotey, F. Cheong-See, D. Arroyo-Manzano, D. McCorry, M. Bagary, L. Mignini, K. S. Khan, J. Zamora, S. Thangaratinam and E. C. Collaboration (2015). "Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis." Lancet **386**(10006): 1845-1852.

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/s/

SILVIA PEREZ-VILAR
11/18/2019 09:52:29 PM

KIRA N LEISHEAR
11/19/2019 07:21:56 AM

SUKHMINDER K SANDHU
11/19/2019 07:22:59 AM

MICHAEL D BLUM on behalf of JUDITH W ZANDER
11/19/2019 08:31:07 AM

MICHAEL D NGUYEN
11/19/2019 08:32:02 AM

ROBERT BALL
11/19/2019 10:48:13 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 15, 2019
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablet, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	SK Life Science, Inc.
OSE RCM #:	2018-2559-4
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 12, 2019 for Xcopri. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Xcopri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and label and labeling memorandums. [abcd]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The established name lacks prominence commensurate with the proprietary name. Per 21 CFR 201.10(g)(2), the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into

[a] Rider B. Label and Labeling Review for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 APR 18. RCM No.: 2018-2559.
[b] Little C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 AUG 08. RCM No.: 2018-2559-1.
[c] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 SEP 23. RCM No.: 2018-2559-2.
[d] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 OCT 31. RCM No.: 2018-2559-3.

account all pertinent factors, including typography, layout, contrast, and other printing features.

3 RECOMMENDATIONS FOR SK LIFE SCIENCE, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Recommendations for the Container Labels and Carton Labeling

1. The established name lacks prominence commensurate with the proprietary name (b) (4) Per 21 CFR 201.10(g)(2), the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

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/s/

CELESTE A KARPOW
11/15/2019 03:59:33 PM

BRIANA B RIDER
11/15/2019 04:30:11 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 6, 2019

To: Philip Sheridan, M.D.
Division of Neurology Products (DNP)

LaShawn Dianat, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for XCOPRI® (cenobamate tablets), for oral use, [controlled substance schedule pending]

NDA: 212839

In response to the DNP consult request dated January 23, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submissions for XCOPRI® (cenobamate tablets), for oral use, [controlled substance schedule pending].

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (LaShawn Dianat) on October 25, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide was sent under separate cover on November 6, 2019.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on October 22, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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/s/

DHARA SHAH
11/06/2019 04:41:10 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 6, 2019
To:	William Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	cenobamate
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 212839
Applicant:	SK Life Science, Inc.

1 INTRODUCTION

On November 21, 2018 SK Life Science, Inc. submitted for the Agency's review an Orignal New Drug Application (NDA) for cenobamate, tablets, for oral use. The purpose of the submission is to seek approval for marketing cenobamate for the treatment of partial onset seizures in adults.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on January 14, 2019, and January 23, 2019, for DMPP and OPDP respectively to review the Applicant's proposed MG for cenobamate, tablets, for oral use.

2 MATERIAL REVIEWED

- Draft XCOPRI (cenobamate) MG received on November 21, 2018 and received by DMPP and OPDP on October 25, 2019.
- Draft XCOPRI (cenobamate) Prescribing Information (PI) received on November 21, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 25, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additonally, in 2008, the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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11/06/2019 11:37:46 AM

LASHAWN M GRIFFITHS
11/06/2019 01:09:25 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 31, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablet, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	SK Life Science, Inc.
OSE RCM #:	2018-2559-3
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 22, 2019 for Xcopri. The Division of Neurology Products (DNP) requested that we review the revised labels and labeling for Xcopri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and label and labeling memorandums.[abc]

2 ASSESSMENT

We reviewed the revised container labels and carton labeling from a medication safety perspective.

(b) (4)

[redacted]

[a] Rider B. Label and Labeling Review for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 APR 18. RCM No.: 2018-2559.
[b] Little C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 AUG 08. RCM No.: 2018-2559-1.
[c] Karpow C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 SEP 23. RCM No.: 2018-2559-2.

(b) (4)

Our review of the revised container labels and carton labeling identified the following areas of needed improvement that may contribute to medication errors:

- The established name lacks prominence commensurate with the proprietary name. Per 21 CFR 201.10(g)(2), the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name.
- (b) (4)

3 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective.

4 4 RECOMMENDATIONS FOR SK Life Science, Inc.

We recommend the following be implemented prior to approval of this NDA:

A. General Recommendations for the Container Labels and Carton Labeling
    1. The established name lacks prominence commensurate with the proprietary name. Per 21 CFR 201.10(g)(2), the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
B. 350 mg daily dose Maintenance Pack Carton Labeling
    1. (b) (4)

       Revise the font color (b) (4) Ensure the color does not overlap with any other colors utilized in highlighting the other strengths or the proprietary name.

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 22, 2019

To: Billy Dunn, MD, Director
Division of Neurology Products

Through: Dominic Chiapperino, PhD, Director
Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Edward Hawkins, PhD, Pharmacologist
Shalini Bansil, MD, Medical Officer
Controlled Substance Staff

Subject: **Product name:** Cenobamate (YKP3089)
Dosages, formulations, routes: immediate release oral tablets tapered up to a maintenance dose of (b) (4) mg once daily
NDA number: 212839
IND Number: 076809
Indication(s): treatment of partial-onset seizures in adult patients
Sponsor: SK Life Science
PDUFA Goal Date: November 21, 2019

Materials Reviewed:

- NDA 212839 for Cenobamate, submitted November 21, 2018, and subsequent amendments
- Statistical review of human abuse potential study (Ran Bi, PhD, Office of Biostatistics, April 15, 2019)

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products (DNP) to evaluate abuse-related preclinical and clinical data submitted by SK Life Sciences (SKSLI) under NDA 212839 and IND 076809 for cenobamate (YKP3089).

Cenobamate has two major mechanisms of action. At therapeutic doses it is proposed to inhibit the fast and slow inactivation of sodium channels by inhibiting the persistent component of the sodium current. However, at 2- to 3-fold the highest therapeutic dose it is a positive allosteric modulator (PAM) of six different types of gamma-amino butyric acid A ($GABA_A$) ion channels. Therefore, it has similar mechanisms of action as other antiepileptics that are controlled in the Controlled Substances Act (CSA) such as benzodiazepines and voltage gated sodium channel modulators (i.e., lacosamide).

Cenobamate is indicated for the treatment of partial onset seizures in adult patients. The drug is designed as orally administered tablets in dosage strengths of 12.5, 25, 50, 100, 150, and 200 mg. Patients are recommended to titrate on to the drug slowly to avoid hypersensitivity reactions to a

maximum tolerated dose of 400 mg. The Sponsor recommends starting at 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. Then, increase the dose every other week by no more than 50 mg once daily to a recommended maintenance dose of (b) (4) mg once daily.

In the NDA submission, the Sponsor proposes to not control cenobamate in the CSA. After evaluating the nonclinical and clinical data in the NDA, CSS concludes that cenobamate has a relative abuse potential lower than substances in Schedule IV but greater than placebo and should be placed into Schedule V of the CSA.

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 212839 for cenobamate and concludes that the drug has abuse potential and should be recommended for placement in Schedule V under the Controlled Substances Act. This conclusion is based on the following data:

- In receptor binding and functional studies, cenobamate blocks voltage gated sodium channels 1.7 ($Na_V1.7$) in the inactive state and is a positive allosteric modulator of $GABA_A$ ion channels.

- In animal general behavior tests, cenobamate produced decreases in locomotor activity, motor function, and increased ataxia.

- In a drug discrimination study in rats, cenobamate partially generalized to the discriminative stimulus effects of midazolam. In a second cenobamate fully generalized to the discriminative stimulus effects of chlordiazepoxide.

- In a self-administration study in rats, cenobamate produced positive reinforcing effects that were significantly greater than placebo.

- In two animal physical dependence studies, chronic administration of cenobamate did not produce signs of withdrawal following drug discontinuation.

- In a human abuse potential (HAP) study, oral administration of cenobamate at the highest therapeutic dose (400 mg) produced statistically significant increases on positive subjective measures such as Drug Liking, Overall Drug Liking, and Good Drug Effects that were greater than those produced by placebo. These subjective responses were less than those produced by the positive control drug alprazolam (1.5 and 3 mg) which is a Schedule IV sedative under the CSA.

- Phase 1 multiple ascending dose studies in healthy subjects showed rates of “euphoria” and “feeling drunk” of about 3% and “disturbance in attention” in about 5% of subjects treated with cenobamate, and these AEs were absent in the placebo group. Abuse-related AEs occurred at high therapeutic and supratherapeutic doses. In Phase 2 and 3 studies abuse-related AEs occur at

low rates in cenobamate treated subjects (0.5-2.5%). These results indicate that abuse-related AEs occur at low rates in cenobamate treated subjects but at rates greater than placebo

- Cenobamate leads to a withdrawal syndrome characterized by insomnia, decreased appetite and weight, and amnesia.

3. Recommendations

Based on the CSS determinations that cenobamate has abuse potential, will have a currently accepted medical use upon NDA approval, but does not appear to produce physical dependence, CSS concludes that:

1. Cenobamate should be recommended for control under the Controlled Substances Act in Schedule V.

2. Section 9 (Drug Abuse and Dependence) should reflect the abuse-related data submitted in the NDA. CSS recommends the following changes to the Sponsor's label, where additions are indicated in bold underlined text and deletions have been stricken through:

9 Drug Abuse and Dependence

9.1 Controlled Substance

TRADENAME contains cenobamate. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration)

(b) (4)

9.2 Abuse

In a human abuse potential study **conducted in recreational sedative abusers (n=39),** single doses of TRADENAME (200 mg and 400 mg) were compared to **placebo** (b) (4) TRADENAME at single doses of (b) (4) 400 mg **produced responses on positive subjective measures such as "Drug Liking," "Overall Drug Liking," "Take Drug Again," and "Good Drug Effects" that were statistically lower than those produced by alprazolam, but statistically greater than the responses produced on these measures by placebo. In this study, euphoric mood occurred** (b) (4) **—Phase 1, multiple ascending dose studies, in healthy subjects, showed rates of euphoria and feeling drunk of about 3% and disturbance in attention** (b) (4) **about 5% in subjects** (b) (4) **In Phase 2 and 3 studies in subjects with epilepsy, euphoric mood, confusional state, and sedation occured at low rates in** (b) (4) **subjects (0.5-2.5%).**

9.3 Dependence

(b) (4)

Clinical studies in healthy subjects indicate that TRADENAME may cause physical dependence and lead to a withdrawal syndrome characterized by insomnia, decreased appetite, depressed mood, tremor, , and amnesia. TRADENAME should be withdrawn gradually *[see Warnings and Precautions (5.4)]*.

II. DISCUSSION

1. Chemistry

The chemical properties of a substance impact the assessment of abuse potential because they determine possible synthetic pathways and methods of administration. An understanding of the chemical properties of a substance may help determine if an individual with a basic knowledge of chemistry can synthesize the substance based upon the availability of the starting materials and complexity of the synthetic path. Furthermore, an understanding of the physicochemical properties of a substance can help predict if a person can produce a solution for injection upon extraction of the active pharmaceutical ingredient, or if the drug can be vaporized or smoked and inhaled. An evaluation of the chemical properties of cenobamate and its known active metabolites is given below.

1.1 Substance Information

Cenobamate is the active pharmaceutical ingredient in immediate release tablets of 12.5, 25, 50, 100, 150, and 200 mg quantities. The tablets are designed for oral consumption with a maximum dose of 400 mg in a 24-hour period. Cenobamate, also known by the developmental codes YKP3089 and PK187 is the nonproprietary name of [(1*R*)-1-(2-clorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate. Cenobamate has a molecular weight of 267.67 g/mol, a chemical formula of $C_{10}H_{10}ClN_5O_2$, and a CAS # of 913088-80-9. Cenobamate is a white to off-white powder that is soluble in organic solvents, sparingly soluble in water (1.7 mg/mL), and has a melting point of 96.8 to 98.3°C (**TABLE 1**).

Table 1: General Chemical Properties of Cenobamate

Nomenclature	
International Non-proprietary Name (INN)	Cenobamate
Chemical Abstract Number (CAS)	913088-80-9
Chemical Name (IUPAC)	[(1*R*)-1-(2-clorophenyl)-2-(tetrazol-2-yl)ethyl] carbamate
Substance codes	YKP3089 and PK187

Structure	
Molecular Formula	$C_{10}H_{10}ClN_5O_2$
Molecular mass	267.67 g mol^{-1}
Structure	
General Properties	
Appearance	White to almost white powder
pKa	none; does not ionize within pH range of 2 – 12.
Solubility (25°C)	Partially soluble in water (1.7 mg/mL), Freely soluble in organic solvents (52.1 mg/mL in methanol)
Melting point	96.8 to 98.3°C
Chirality/Stereochemistry	synthesized as purely the *R*-enantiomer

Cenobamate is synthesized [redacted] (b) (4)

Excipients in the tablet

Cenobamate contains a series of excipients [redacted] (b) (4) The excipients and their functions are listed in **Table 2**. The excipients in cenobamate do not have a known abuse liability.

Table 2: Composition of Excipients Used to Manufacture Cenobamate

Component	**Function**	**Quantity**	
		12.5 mg	**200 mg**
Cenobamate	[redacted] (b) (4)		
Microcrystalline Cellulose (b) (4)			
Lactose Monohydrate			
Sodium Starch Glycolate			
Colloidal Silicon Dioxide			
Magnesium Stearate			
Tablet Core Weight			

1.2 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

The Sponsor is not seeking abuse-deterrent labeling and did not conduct in vitro manipulation and extraction studies on the to-be-marketed formulation. Dissolution and disintegration studies conducted by the Sponsor indicate that cenobamate is slightly soluble in water at pH ranges of 2 to 12 and is soluble to freely soluble in common organic solvents such as ethanol.

2. Nonclinical Pharmacology

Receptor binding and activity assays can give an indication as to whether or not a substance affects a receptor pathway that is known to be associated with abuse potential. For substances that are CNS active, the Sponsor is required to determine if their active pharmaceutical ingredient and any major metabolites will bind to and have activity at these receptors. The Sponsor conducted binding and activity studies on cenobamate. The data, summarized below, indicate that cenobamate is a sodium channel blocker and a positive allosteric modulator (PAM) of gamma-aminobutyric acid (GABA)-A gated chloride channels.

2.1 Receptor Binding and Functional Assays

The Sponsor conducted a series of binding studies (Study numbers SK16016; 1076805; 1023568; Pharm-NJ-SM-19; Pharm-SK-YC-01) to determine if cenobamate binds significantly to receptors, ion channels, or transporters that are known to be associated with abuse potential. Significant responses in in vitro binding studies are defined as ≥ 50% inhibition or stimulation of control specific binding. In this study the dose response range of cenobamate was 0.3, 1, 3, 10, 30, 100, 300, and 1000 µM. The data presented in **Table 3** indicate that cenobamate binds to the adrenergic β1 receptor, GABA-gated chloride channel, dopamine transporter, kappa-opioid receptor, and the orexin 1 receptor. However, the Sponsor used doses 10 to 100-fold higher than that recommended by the guidance for industry, Assessment of Abuse Potential of Drugs (10 µM), and this resulted in positive in vitro binding data from concentrations of cenobamate that would not be expected in vivo. Binding at the dopamine transporter, kappa-opioid receptor, and orexin receptor are not expected based on the inability of cenobamate to reach these free steady state concentrations in the CNS. Studies conducted on the cannabinoid 1 receptor (CB1) (Study # 100007197), CB2 receptor (Study # AB57467) 5-HT1A receptor (Study # 18488), 5-HT2C receptor (Study # 100007197), 5-HT3A receptor (Study # 160629.TLI), and the mu opioid receptor (Study # AB57467), indicate that cenobamate does not bind to these receptors.

Table 3: Cenobamate Specific Receptor Binding Targets

Receptor/ Molecular Target	**IC_{50} (µM)**	**K_i[1] (µM)**
Adrenergic β_1	370	210
Cl^- channel (GABA-gated)	300	250
Dopamine transporter	710	380
Kappa-opioid receptor	950	640
Orexin receptor (OX1)	550	540

The Sponsor performed a follow-up, in vitro activity study on the β_1 adrenergic receptor and the GABA-gated chloride channel. Study # SK17001 indicated that cenobamate had no agonist activity at the β_1 adrenergic receptor and produced antagonist activity at doses that are not easily attenable in vivo (IC_{50}[2] range 370 – 910 µM). In the studies to assess the activity of cenobamate at different subtypes of the human $GABA_A$ channels (Study numbers SK17002, and SK17005) electrophysiological assays were conducted to determine if cenobamate was an agonist, antagonist, or a positive allosteric modulator (PAM) at these ion channels. Cenobamate increased $GABA_A$ currents only in the presence of GABA, indicating that it acts as a PAM, similar to benzodiazepines. The EC_{50}[3] values presented in **Table 4** indicate that the drug is much less potent at the $GABA_A$ channel than marketed benzodiazepines.

Table 4: EC_{50} (µM) of Cenobamate at Various Human $GABA_A$ Channels

$GABA_A$ channel subtype	**EC_{50} (µM)**	**RO15-4513 EC_{50} (µM)**	**Diazepam EC_{50} (µM)**	**Study #**
α1β2γ2	192	--	--	SK 17002
α2β3γ2	119	--	12	SK 17005
α3β3γ2	194	--	81	SK 17005
α4β3γ2	42	15	--	SK 17005
α5β3γ2	89	--	18	SK 17005
α6β3γ2	58	68	--	SK 17005

The Sponsor determined that the major mechanism of action of cenobamate is through blockade of voltage gated sodium channels (Na_v) which are sensitive to changes in voltage across a cell membrane which regulate their different states; open, inactive, and closed states. Several drugs have been found to have greater affinity to different states of ion channels because of accessibility to different binding sites within the pore of the channel (Hille, 2001). Study # 06P0013 used HEK-293 cells stably transfected with human $Na_v1.7$ channels and found that cenobamate was much more potent as a channel blocker in the inactive state producing an IC_{50} of 2.81 µM compared to an IC_{50} of > 0.4 mM in the tonic or use-

[1] K_i – The inhibitory constant is a measure of the binding affinity of a substance to its substrate or receptor

[2] IC_{50} – The half maximal inhibitory concentration to a substance

[3] EC_{50} – The half maximal stimulatory concentration of a substance to produce a specific biological function

dependent states. This study determined that cenobamate exerts a concentration dependent block of $Na_v1.7$ channels by binding to them in their inactive state. This study was followed by Study SK11011 which produced similar results using cenobamate and active comparators on the current elicited by the $Na_v1.7$ ion channel. Cenobamate produced state dependent inhibition of the $Na_v1.7$ channel with an IC_{50} of 26 µM compared to lamotrigine (IC_{50} of 23 µM), lidocaine (IC_{50} of 7.1 µM), and carbamazepine (IC_{50} of 19 µM), none of which are currently controlled in the U.S.

Metabolites of cenobamate

There are no major active circulating metabolites of cenobamate.

Conclusion

In vitro studies indicate that cenobamate functions as a $Na_v1.7$ channel blocker with secondary activity as a PAM of $GABA_A$ channels. Lacosamide is an antiepileptic drug currently listed in Schedule V that is a Na_v blocker, albeit through a different mechanism of action and without $GABA_A$ activity. $GABA_A$ PAMs, such as the barbiturates and benzodiazepines are typically associated with abuse potential and are controlled in various schedules of the CSA.

2.2 Safety Pharmacology/Metabolites

Absorption

The absorption of cenobamate was assessed in multiple species after single and repeated administration. The review of the data in this section will focus on the studies that are most relevant to the assessment of the abuse potential of cenobamate and include studies that were conducted in mice, rats, and nonhuman primates.

Study # DMPK 07-01 was conducted to determine the PK parameters of a single dose of cenobamate at 20 mg/kg PO or IV in male CD-1 mice. The data in **Table 5** indicate that cenobamate is well-absorbed orally with a bioavailability of 59.6%. As expected, the C_{max} from the IV method of administration is approximately 3.5-fold higher than that from oral administration and the exposure is almost double, however, both methods of administration produce a half-life of 2 hours.

Table 5: PK Parameters of a Single 20 mg/kg Dose of Cenobamate PO or IV in Male CD-1 Mice

Dose	20 mg/kg	
male CD-1 mice	PO	IV
C_{max} (µg/mL)	13.3	47.9
t_{max} (h)	4	-
AUC_{24} (µg*h/mL)	113	191
$t_{1/2}$ (h)	2.1	1.9
CL (L/kg/h)	-	0.105
Bioavailability (%)	59.6	-

The Sponsor then conducted a similar study in CD-1 rats (Study # DMPK 05-01) in which the animals were administered a single dose of cenobamate at 15 mg/kg PO or IV (**Table 6**). The bioavailability of cenobamate in rats is almost twice as high as the bioavailability of the drug in mice. It produced a C_{max} of 16.9 µg/mL PO and 13.3 µg/mL IV and a total exposure of 135 µg*h/mL PO compared to 113 µg*h/mL IV. Similar to the mouse, cenobamate had a half-life of two hours in the rat and a t_{max} of 5 hours.

Table 6: PK Parameters of a Single 15 mg/kg Dose of Cenobamate PO or IV in CD-1 Rats

Single administration	dose of 15 mg/kg	
Male CD rats	PO	IV
Cmax (µg/mL)	16.9	13.3
tmax (h)	5	-
AUCt (µg*h/mL)	135	113
t1/2 (h)	1.98	1.9
CL (L/kg/h)	-	0.13
Bioavailability (%)	119.4	-

The Sponsor then conducted a study (Study # 06D0021) in which they administered male and female Sprague-Dawley (SD) rats cenobamate at 15 mg/kg or 60 mg/kg subcutaneously (SC) or 15 mg/kg or 40 mg/kg through intraperitoneal (IP) administration. The only sex-related differences appear to be at the higher 40 mg/kg or 60 mg/kg doses where females tend to have higher exposure, a longer t_{max}, and significantly longer half-life with no change in the C_{max} (**Table 7**). This suggests that female rats metabolize the drug more slowly leading to increased half-life and exposure. All of the abuse-related behavioral studies were conducted in male SD rats and produced positive subjective effects.

Table 7: PK Parameters of a Single 15 or 60 mg/kg Dose of Cenobamate Administered SQ or IP in SD Rats

Single administration	Subcutaneous (SQ)				Intraperitoneal (IP)			
Dose	15 mg/kg		60 mg/kg		15 mg/kg		40 mg/kg	
Sprague Dawley rats	M	F	M	F	M	F	M	F
C_{max} (µg/mL)	13.3	12.4	44.6	45.5	12.5	14.4	36.2	38.3
t_{max} (h)	1.8	1	7.2	9.2	0.7	0.4	0.6	2.7
AUC_{24} (µg*h/mL)	154	170	705	847	132	202	455	699
$t_{1/2}$ (h)	6.81	6.78	4.31	11.1	5.28	11	4.49	23

In Study # 030157 PK parameters were determined after single doses of cenobamate at 15 mg/kg were administered PO or IV to male and female nonhuman primates (Cynomolgus monkeys). Interestingly, the results of this study were counter to that of the rat study in that male monkeys appear to have greater bioavailability, C_{max}, AUC, and much greater half-lives compared to female monkeys through both methods of administration (**Table 8**). It appears from this study that male monkeys absorb cenobamate more quickly (t_{max}) and have a half-life ten hours longer compared to females.

Table 8: PK Parameters of a Single 15 mg/kg Dose of Cenobamate Administered Orally (PO) or Intravenously (IV) in Cynomolgus Monkeys

Single administration	Oral		Intravenous	
Dose	15 mg/kg		15 mg/kg	
Cynomolgus Monkeys	M	F	M	F
C_{max} (µg/mL)	31.5	26.7	34.6	32.4
t_{max} (h)	2.33	3.33	0.26	0.33
AUC_{24} (µg*h/mL)	436	359	420	389
$t_{1/2}$ (h)	22.7	13.4	26.7	16.5
CL (L/kg/h)	-	-	0.018	0.026
Bioavailability (%)	110	83.9	-	-

The data in **Table 9** indicate that male Cynomolgus monkey maintain the greater Cmax and almost double the exposure at the steady state compared to their female counterparts after repeated administration of cenobamate. Data from studies # SK17007 and #SK07/037 indicate that after 14 days of oral administration of 18 mg/kg cenobamate male rats have an AUC of 633 µg*h/mL compared to the females 395 µg*h/mL. After one-year male Cynomolgus monkey have two-fold the C_{max} of their female counterparts, 61.8 µg/mL to 36.9 µg/mL respectively, and a similar two-fold difference in AUC, 1049 µg*h/mL to 542 µg*h/mL respectively.

Table 9: PK Parameters at Steady State After 52 Weeks of Oral Administration in Cynomolgus Monkeys

	Oral (Day 1)		**Oral (Day 14)**		**Oral (Week 52)**	
Dose	18 mg/kg		18 mg/kg		18 mg/kg	
Cynomolgus monkey	M	F	M	F	M	F
Cmax (µg/mL)	27.7	21.5	38.6	27.2	61.8	36.9
tmax (h)	8	4	1.5	2	3.5	4
AUCt (µg*h/mL)	528	365	633	395	1049	542

Distribution

Study 0830RS62.002 was conducted to determine the distribution of radio-labeled cenobamate in Sprague Dawley rats after oral administration.

A single oral dose of cenobamate (15 mg/kg or 45 µCi/kg) was given to male rats that were sacrificed 1, 4, 12, 24, or 48 hours after dosing. In the CNS, detectable levels of radioactivity were measured up to 12 hours ($C_{max} \leq 16.45$ µg eq/g). The highest levels of radioactivity were measured in the kidney ($C_{max} \leq 35.26$ µg eq/g) indicating that lasmiditan or its metabolites are most likely excreted renally. The CNS, liver, lung, and kidney all showed higher levels of radioactivity than blood (at the 1 hr timepoint), however low levels of radioactivity were measured in the testis, epididymis, ovaries, and uterus.
The Sponsor also conducted two in vitro protein binding studies; Study # Metab 2004-01 and Study # SK16009. In human plasma, cenobamate protein binding was concentration dependent over a concentration range of 0.114 to 11.414 µg/mL with a mean binding of 59.14%. At a concentration of

1.1 µg/mL human plasma had a mean unbound fraction of 39%, compared to 45% in rat, 56% in mouse, and 64% in rat. In monkeys there was no evidence of concentration dependent binding over a concentration of 0.5 to 50 µg/mL with percent unbinding ranging from 30 to 40%. Overall these studies indicate that cenobamate has moderate binding to plasma proteins.

Metabolism

The metabolism of cenobamate was determined using in vitro and in vivo studies.

In vitro studies (Study #s 03-SKBP.P01R1, SK12006, and SK11004) were conducted using liver microsomes of human, dog, and rat in order to determine and compare the major metabolites in these species. These studies suggest that after 1 hr incubation of 500 µM there is very slow metabolic turnover of cenobamate with CYP enzymes. Furthermore, CYP2E1, 2A6, and 2B6 are most likely involved in the oxidative metabolism of cenobamate to produce a monohydroxylated metabolite. A glucuronide metabolite catalyzed by UGT2B7 was also detected in human liver microsomes. These studies did not determine the overall amounts of metabolite that were detected.

The in vivo metabolism studies were conducted in mice, rats, rabbits, monkeys, and humans, using the oral method of administration. Study SK14007 was a mass balance study that compared the metabolites in the previously listed species. This study determined that cenobamate is metabolized through two major pathways: 1) N-glucoronidation, accounting for 39% of the dose, and 2) oxidation of the aromatic ring followed by glucoronidation, accounting for 37% of the dose. A total of eight metabolites were identified in human excreta, M1, M2a, M2b, M3, M6 and M7 (isomers), M5, and M11. In human plasma 98% of the drug was left unchanged. No major metabolites were detected in the mouse and the major metabolite detected in the rat was M6 (urine) after 8 hours. In monkeys the major metabolite was the M1 metabolite detected at 35% in urine and 11% in feces. These data indicate that nonhuman primates produce a similar metabolite profile as humans which is different from that produced in rats. Since the Sponsor determined that humans do not produce any major circulating metabolites (Study # AA41857) it won't be necessary for further abuse related studies to be conducted on metabolites.

Excretion

The Sponsor also conducted five excretion studies in mice, rats, rabbits and monkeys (cynomolgus) (Study numbers SK08017, 0830RS62.001, SK08016, SK08018, SK07/062). In rats, following a single oral dose of 15 mg/kg (45 µCi/kg), 59% was excreted in the urine and 48% in the feces in males. In male monkeys, following a single oral dose of 15 mg/kg (45 µCi/kg), 62% in the urine and 15% in the feces with a total mean recovery of 94% with 72 hours of dosing.

Conclusion

The absorption of cenobamate in rodents is dependent on dose and method of administration. In rats, cenobamate is highly orally bioavailable (119%), however, it has a long t_{max} (5 hrs PO, 1.8 – 7.2 hrs SQ, and 0.7 – 0.4 hrs IP, male to female), and a long half-life that appears to be dependent on dose and method of administration. The oral half-life at 15 mg/kg is 1.98 hours, SQ is 6.8 hours, and IP is 5.2 – 11 hours. Furthermore, at higher doses (60 mg/kg) female rats have great exposure of the drug with much longer half-lives than the male rats. The opposite is seen in monkeys in which the males had

longer half-lives and greater exposure than the females through both oral and IV methods of administration. These sex differences were maintained at steady state in the monkey. These sex differences were not detected in human PK parameters in study clinical Study # AA24143 (**Table 13**).

The distribution, metabolism, and excretion of cenobamate indicate that the drug permeates into the CNS, does not produce major circulating metabolites in humans and is mostly excreted renally with about 1/3 being detected in the feces.

2.3 Findings from Safety Pharmacology and Toxicology Studies

Safety Studies

The Sponsor conducted two animal studies to assess the cardiovascular and respiratory safety pharmacology of cenobamate. Study 1259SS62.001 assessed the effects of cenobamate on cardiovascular function and ECG in conscious telemetered male Cynomolgus monkeys. Four monkeys each received an oral dose of 4, 12, or 36 mg/kg cenobamate and their cardiovascular function was monitored 15 minutes predose to 24 hours postdose. The study determined that there were no significant cardiac effects (electrocardiograms) or effects on circulatory function (heart rate, diastolic, systolic, and mean arterial pressure) at any of the doses tested.

Study aa25489 was then conducted to assess the respiratory effects of cenobamate in male rats. A single dose of drug at 10, 30, or 60 mg/kg was orally administered, and the rats were monitored for respiratory rate, tidal volume, and minute volume for 24-hours post dose. Only the high dose of 60 mg/kg produced a significant effect producing a maximum peak effect of 20% reduction in minute volume during the recording period. The positive control, sodium pentobarbital, produced the expected significant changes in respiratory effects thereby validating the study.

Toxicity Studies

The Sponsor also conducted a series of single and repeat dose toxicological studies of cenobamate in mice, rat, rabbit, and cynomolgus monkey. **Table 11** presents an overview of the toxicological studies conducted in mice (CD-1), rats (Sprague Dawley), and monkeys (Cynomolgus monkey) as these animals are the most relevant in the studies conducted by the Sponsor to address the abuse potential of cenobamate. The data included in these studies include behavioral assessments, pharmacokinetic data, and a necropsy which consisted of tissue distribution and examination of gross morphological changes. In single dose studies the Sponsor determined that a lethal oral dose in rats equated to 300 mg/kg which killed all of the rats given this dose. A single oral dose of cenobamate between 45 and 250 mg/kg produced adverse events consisting of uncoordinated gait, decreased activity, hyperthermia, muscle weakness, ataxia, and shallow breathing at doses of 200 mg/kg and higher.

Repeat dose toxicity studies with cenobamate were conducted in mice (CD-1), rats (Sprague Dawley), and nonhuman primates (Cynomolgus monkey). The studies ranged from 5 days in the mouse to 52 weeks in nonhuman primates. In the mouse, 100 mg/kg/day for 5 or 14 days produce decreased activity and uncoordinated gate. In the rat, similar effects were seen at doses of 60 mg/kg/day (28 days) and at 24 and 48 mg/kg/day (13 weeks). Many of the same deleterious effects were seen in nonhuman primates at doses of greater than 12 mg/kg/day at time frames above 28-days. Labored respiration was

seen at doses of 18 mg/kg/day in a 52-week study or 120 mg/kg/day in a 7-day study. The doses at which many of these effects were seen were in the supratherapeutic range producing PK values 2 to 4-fold higher than those of the therapeutic dose (Sections 2.2 Safety Pharmacology/Metabolites and Section 3.1 Clinical Pharmacology).

In conclusion, both the single and repeat dose toxicity studies produced behaviors that are consistent with depressant drugs that positively modulate $GABA_A$ receptors.

Table 10: Overview of Toxicological Studies in Animals using Cenobamate

Study #	Single/Repeat	Dose (mg/kg)	Species (Strain)	Adverse Event
1004-1175	single	0, 10, 30, 90, 130	Mouse (CD-1)	130 mg/kg - uncoordinated gait, decreased activity, hyperthermia
Pharm-NJ-RG-08	single	0, 100, 150, 200	Mouse (CD-1)	MTD = 150 mg/kg; >100mg/kg - uncoordinated gait, decreased activity, muscle weakness, shallow breathing (200 mg/kg)
Pharm-NJ-RG-10	single	0, 200, 250, 300	Rat (Sprague Dawley)	LD = 300 mg/kg; 250 mg/kg - decreased activity, ataxia, muscle weakness, ptosis, loss of righting reflex
3004-0761	single	150	Rat (Sprague Dawley)	150 mg/kg - severe hypoactivity, uncoordinated gait, tremors, animals euthanized
1004-1161	single	0, 1, 5, 15, 45	Rat (Sprague Dawley)	45 mg/kg - weakness, uncoordinated gate, loss of righting reflex
SK09002	repeat (5 day)	100, 150	Mouse (CD-1)	> 100 mg/kg/day - decreased activity and uncoordinated gait
SK09004 & SK09024	repeat (14 day)	0, 30, 60, 120	Mouse (CD-1)	> 100 mg/kg/day - decreased activity and uncoordinated gait
1004-1151	repeat (28-day)	10, 30, 100/60	Rat (Sprague Dawley)	> 60 mg/kg/day - loss of righting reflex, uncoordinated gait, decreased activity
SK07/038	repeat (13 weeks)	12, 24, 48	Rat (Sprague Dawley)	> 24 mg/kg/day - loss of righting reflex, uncoordinated gait, decreased activity
1003-2053	repeat (7-days)	120	Cynomolgus Monkey	vomiting, incoordination, hypoactivity, labored respiration, tremors, convulsions
2004-0143	repeat (14 day)	0, 10, 30, 60	Cynomolgus Monkey	> 30 mg/kg/day - slight decrease in activity, vomiting, uncoordinated gait
SK07/055	repeat (14 day)	24, 30	Cynomolgus Monkey	24 mg/kg/day - tremors; 30 mg/kg/day-incoordination, weakness, gait
1004-0743	repeat (28-day)	4, 12, 36/24	Cynomolgus Monkey	> 12 mg/kg/day - labored respiration, uncoordinated gait, weakness, drowsiness

SK07/037	repeat (52 week)	3, 9, 18	Cynomolgus Monkey	18 mg/kg/day - labored respiration, uncoordinated gait, weakness, drowsiness

2.4 Animal Behavioral Studies

Several types of in vivo behavioral studies are used to ascertain the reinforcing effects and pharmacodynamic effects of a drug. These studies help to determine whether or not a substance has abuse potential and to what pharmacological class of drugs the substance is most similar.

General CNS effects

Mice

The Sponsor conducted four studies to assess the locomotor activity of animals given cenobamate. The following studies PHARM-NJ-GF-03, PHARM-NJ-GF-01, PHARM-NJ-SM-03, and PHARM-DIT-YS-12 were conducted in CF-1 or ICR mice. The studies tested doses of 10, 15, 30, 50, or 60 mg/kg either PO or IP and the last study used diazepam as a positive control. In general, the studies indicate that cenobamate produces a significant decrease in locomotor activity at doses above 30 mg/kg. In the last study, a dose of 50 mg/kg IP produced an ED_{50} of 47.25 (0.7 – 93.8) mg/kg compared to the ED_{50} of diazepam of 2.78 (0.95 – 4.61) mg/kg.

The Sponsor also conducted three rotarod studies (Study #'s PHARM-DIT-YS-13, NO1-NS-4-2359, and PHARM-NJ-SM-12) to measure balance and motor coordination after administration with cenobamate in mice. Male CF1 mice were used in all three studies and were administered a range of doses of 45, 50, 60, 70, 75, or 80 mg/kg cenobamate IP or 80, 90, 100, or 120 mg/kg PO. Although the studies were conducted with slight differences the outcomes were the same. The toxic dose (TD) is determined as the point at which animals loose motor function or balance and fall off the rotating rod during a 1-minute test session at specific time points after administration of the drug (e.g., 0.25, 0.5, 1, and 2 hours). After IP administration the TD_{50}[4] was calculated to be 55.7 mg/kg in one study and 52 mg/kg in the other study. The TD_{50} after oral administration was determined to be 85.6 mg/kg.

The potentiation of ethanol-induced anesthesia by cenobamate was measured in CF-1 mice (Study # pharm-nj-sm-06). This study was conducted to determine if cenobamate produces hypnotic and sedative effects similar to benzodiazepines such as diazepam. Animals were given cenobamate at 10, 30, 60, or 100 mg/kg PO, diazepam at 4 mg/kg PO, or vehicle. One hour afterwards they were given a nonhypnotic dose of ethanol (3 g/kg IP). After 45 minutes the animals were then tested in the loss of righting reflex challenge to determine their ability to right themselves after being placed on their back. Cenobamate produced a dose dependent loss of righting reflex with no effect at 10 mg/kg and seven of eight mice losing the ability to right themselves at the highest dose of 100 mg/kg. Diazepam, at a dose of 4 mg/kg, produced a loss of righting reflex in 6 out of 10 mice whereas none of the vehicle treated

[4] TD_{50} – the dose of a drug at which toxicity is determined to occur in 50% of the cases based on the measured parameter.

animals lost the ability to right themselves. As a result, cenobamate dose dependently potentiates ethanol-induced anesthesia in mice similar to diazepam.

Rats

Similar to the rotorod studies in mice, the Sponsor also conducted three rotorod studies in rats. Studies PHARM-DIT-YS-16 and PHARM-NJ-RG-07 used Sprague-Dawley rats and Study # SK07/036 used CD IGS rats. In the first two studies the rats were dosed with 100, 200, or 250 mg/kg cenobamate PO and in the third study the rats received 10, 30, 100, or 300 mg/kg cenobamate PO. The first two studies had similar results producing TD_{50s} of 195.7 mg/kg and 244.4 mg/kg respectively. However, the third study produced a TD_{50} of 101.6 mg/kg. The lower TD_{50} may be the result of the lower doses utilized in the study, skewing the dose response curve to the left.

The Sponsor also conducted two Irwin screens[5] to assess the autonomic, behavioral, and motor systems after administration of cenobamate in Sprague-Dawley rats. In Study # pharm-nj-sm-13 animals were divided into five groups designated as naïve, vehicle, 200, 250, and 300 mg/kg cenobamate PO. Animals were then observed in a battery of tests 0.5, 1, 2, and 5 hours post administration. In this study, there were no lethalities in the naïve or the vehicle treated groups, there was one of six in the 200 mg/kg group, five of six in the 250 mg/kg group, and three of six in the 300 mg/kg group. Therefore, the maximum tolerated dose (MTD) in rats was determined to be 200 mg/kg cenobamate PO. The loss of animals may have severely compromised the statistical determinations of the effects of the drug, therefore, the Sponsor conducted another study (Study # pharm-nj-sm-14) at doses of 10, 30, and 100 mg/kg. No deaths were observed with the lower doses of cenobamate. Animals at all of the tested doses had a significant decrease in body temperature with the largest decrease of -2.5°C five hours after administration of 100 mg/kg cenobamate PO. Consistent with previous studies in mice, the rats also demonstrated a significant decrease in locomotor activity, motor function, and increased ataxia in the 100 mg/kg group. Although a positive control was not used in either study, these neurological effects are consistent with those of $GABA_A$ PAM's (Roux et al., 2005).

The Sponsor also tested for the effects of cenobamate on intestinal transit, the inhibition of which can be a sign of mu opioid receptor agonist activity (Bueno and Fioramonti, 1988). In this study, male Sprague-Dawley rats were administered single doses of cenobamate at 0, 10, 30, or 60 mg/kg PO, or morphine 20 mg/kg SC as a positive control. A dose of 30 mg/kg produced a significant reduction in intestinal transit of 17% and a dose of 60 mg/kg produced a significant reduction of 15% compared to the morphine control which reduced transit by 74%. Although cenobamate did produce a significant decrease in intestinal mobility, the binding data from Study # AB57467 indicate that cenobamate does not bind to the mu opioid receptor. Evidence indicates that cenobamate's modulation of $GABA_A$ channels may be responsible for these effects in the gastrointestinal system (Auteri et al., 2015).

Self-administration

[5] Irwin S (1968) Comprehensive observational assessment: Ia. A systematic, quantitative procedure for assessing the behavioral and physiologic state of the mouse. *Psychopharmacologia* **13**:222-257.

A self-administration assay is an experimental paradigm in which animals identify if a substance has positive reinforcing effects. Positive reinforcement occurs when the presentation of a desired stimulus results in an increase in behavior that is associated with the administration of the desired stimulus (Gauvin et al., 2017). For example, for abuse assessment purposes, animals are first trained to press a lever (behavior) resulting in the administration (typically IV) of a training drug (desired stimulus) known to be a drug of abuse (e.g., cocaine). Once properly trained, the animals undergo an extinction test to confirm that the training drug is the stimulus responsible for the reinforcing effects and not some other cue in the assay. Animals then receive test drug, and rates of lever pressing and rates of injections are measured. If the rates of administered drug are significantly different from placebo and the animals are not motor impaired by the drug, as measured by rates of lever pressing, the drug is said to be self-administered (Gauvin et al., 2017).

Study SK13025 was a self-administration study conducted in male Sprague Dawley rats to assess the reinforcing effects of cenobamate compared to midazolam (CIV). Animals were trained to self-administer food on a fixed ratio 5 (FR5) schedule of reinforcement. After acquisition of the task, animals were surgically implanted with indwelling catheters and trained to IV administer 0.0125 mg/kg/inj midazolam in a 1 hr session under an FR5. The Sponsor tried to test doses of 0.02, 0.08, 0.2, 1, and 2 mg/kg/inj of cenobamate, however the 1 and 2 mg/kg doses were not tested because of issues with solubility. The animals were tested on each dose of cenobamate for 5 consecutive days with a 1-week training session of midazolam between each dose. The results of the study indicate that at the training dose of midazolam of 0.0125 mg/kg/inj the mean number of infusions (6.8 (0.55)) were significantly greater than saline (3.6 (0.11)). All other doses of the midazolam dose response curve did not produce a mean number of infusions greater than saline and midazolam response rates appeared to decline over time. This may be because midazolam caused the animals to fall asleep or be lethargic at the higher doses. Similarly, the mean number of infusions (5.0 (0.41)) at the 0.08 mg/kg/inj dose of cenobamate was also significantly greater than the mean number of saline infusions. However, the other cenobamate doses tested, 0.02 and 0.2 mg/kg/inj, did not produce a mean number of injections that was significantly different from saline ((4.8 (0.45) and 4.9 (0.42) respectively). It should be noted that despite the increasing dose, the number of infusions remained nearly unchanged and were significantly lower than the mean number of midazolam training dose infusions.

The Sponsor also conducted an extension to this study because of the long half-life of cenobamate in animals with a range of 2-12 hours (2 hrs after IV administration). In order to account for possible accumulation of the drug because of the long half-life, the Sponsor conducted a study over a 22-hour test session using a progressive ratio (PR) design. A PR design increases the number of responses between each injection of drug in order to receive the next injection. This study did not provide useful results because the positive control, midazolam, did not differ significantly from saline. Cenobamate also did not differ significantly from saline although high variability in the mean response rates is noted.

The pharmacokinetic parameters measured in a self-administration study are difficult to interpret and are hindered by the time points at which blood/plasma can be obtained from the animal. In order to rely on the PD measurements of the study, the animals cannot be manipulated until the conclusion of the test session and therefore, blood samples were obtained at the 1 hr timepoint. For cenobamate, the mean rat plasma measurements at the 0.02 mg/kg/inj dose were below the level of quantification. The plasma concentrations at the one-hour time point for the 0.08 and the 0.2 mg/kg/inj doses were 151 and 611

ng/mL respectively. This is much lower than the expected C_{max} of 24 μg/mL in humans from a therapeutic dose of 200 mg/mL.

In conclusion, cenobamate at a dose of 0.0125 mg/kg/inj yielded a significant response indicative of a reinforcing effect. Response rates were not significantly affected at this dose. All of the cenobamate responses were also significantly lower than the positive control midazolam.

Drug Discrimination

Drug discrimination is an experimental method in which animals identify whether a test drug produces physical or behavioral effects (an interoceptive response) similar to those produced by another drug with known pharmacological properties. If the known drug is one with abuse potential, drug discrimination can be used to predict if a test drug will have abuse potential in humans (Balster and Bigelow, 2003). For abuse assessment purposes, an animal is first trained to press one bar when it receives a known drug of abuse (the training drug) and another bar when it receives placebo. A challenge session with the test drug determines which of the two bars the animal presses more often, as an indicator of whether the test drug is more like the known drug of abuse or more like placebo. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing $\geq$80% on the bar associated with the training drug (Sannerud and Ator, 1995; Doat et al., 2003). A test drug that generalizes to a known drug of abuse will likely be abused by humans (Balster and Bigelow, 2003).

Study SK13026 was conducted to evaluate the discriminative stimulus effects of cenobamate compared to midazolam, a Schedule IV benzodiazepine. Male Sprague Dawley rats were trained to discriminate orally administered 3 mg/kg midazolam from vehicle in a two-lever choice procedure for a food reward. After the training procedure animals achieved a mean lever correct responding of 99.3% with 2.9 responses/sec for 3 mg/kg midazolam and 99.5% with 2.5 responses/sec for vehicle. Animals then moved to the testing phase in which a dose response curve to midazolam was conducted using 0, 1, 1.7, 3, or 10 mg/kg midazolam PO administered 30 minutes prior to the testing session. Animals given vehicle did not respond for midazolam training cue, those that received 1 or 1.7 mg/kg midazolam partially generalized to the training cue and those that received 3 or 10 mg/kg fully generalized to the midazolam training cue. Animals were then given cenobamate at doses of 0, 2, 8, 20, 60, or 180 mg/kg PO and placed in the chamber 4.5 hours after administration of the drug. Cenobamate at 0, 2, 8, or 20 mg/kg did not substitute for the training cue of midazolam at any of these doses with percent responding and response rates of 0.6%; 2.7 responses/seconds, 0.4%; 2.9 responses/seconds, 0.5%; 3.0 responses/seconds, or 9.5%; 2.5 responses/seconds respectively. The higher doses of cenobamate, 60 and 180 mg/kg produced partial generalization to the midazolam cue with percent responding and response rates of 43.6%; 2.2 responses/seconds and 64.1%; 0.7 responses/seconds respectively. The response rates at the 180 mg/kg dose were reduced considerably, indicating that the animals were severely compromised by that dose of drug. Diazepam was the positive control used in this study and administration of 0, 0.3, 1, or 3 mg/kg produced no generalization at the 0 to 1 mg/kg doses and partial generalization at the 3 mg/kg dose (70.9%; 3.3 responses/second).

The Sponsor expanded on this study by testing the cenobamate cue at 8, 12, and 24 hours because of the long half-life of the drug (~ 5 – 11 hours in rats **Tables 6 and 7**) (compared to the midazolam cue at 0.5 hours). The rats were given 20 mg/kg of cenobamate PO and produced the following results: 8 (10.4%;

3.2 responses/seconds), 12 (19.5%; 3.0 responses/seconds) and 24 (0.2%; 3.6 responses/seconds) hours indicating that they did not generalize to the midazolam cue at these longer timepoints.

Exposure to cenobamate in this study ranged from the proposed therapeutic to 3 to 8-fold the highest therapeutic dose of 400 mg. In rats, single administration of 2, 8, 20, 60, or 180 mg/kg cenobamate produced C_{max} values of 1.83, 7.81, 17.5, 36.5, and 80.1 µg/mL, and AUC_{24} values of 19.8, 100, 241, 623, and 1090 µg*hr/mL respectively. A single dose of 400 mg/kg cenobamate PO in humans produced a C_{max} of 10.3 µg/mL and an AUC of 750 µg*hr/mL (Study # AA22780).

In conclusion, cenobamate partially substituted for the discriminative stimulus effects of midazolam at doses of 60 and 180 mg/kg with the 180 mg/kg dose having significantly decreased response rates. Lower doses 0, 2, 8, and 20 mg/kg did not generalize to the midazolam cue. This is in concordance with the in vitro binding and activity data indicating that higher doses of cenobamate are necessary to activate the $GABA_A$ effects of the drug (Section 2.1).

The Sponsor also conducted study # SK16005 to compare the discriminative stimulus effects of cenobamate against a panel of other drugs of abuse that represent different drug classes. These drugs were 2,4-dimethoxy-4-iodoamphetamine (DOI) (a hallucinogen), d-amphetamine (a stimulant), morphine (an opioid), chlordiazepoxide (CDP) (a benzodiazepine), and CP 55,940 (a cannabinoid). Separate groups of rats were used for each drug. In this study, cenobamate did not engender cross generalization to DOI, morphine, or CP 55,940 as expected based on the different mechanisms of action that these drugs produce. Partial generalization was detected with d-amphetamine (0.32 mg/kg IP) with 20 mg/kg cenobamate IP, however, this was only detected 20 min post-dose and not at the later time points when cenobamate is expected to be at its T_{max}. Cenobamate did engender full generalization to the CDP cue that was both dose (20 and 30 mg/kg IP) and time dependent. However, this effect only occurred at the 20-minute time point and not at the 4, 8, or 12-hour time points. Single IP administration of cenobamate produced C_{max}, t_{max} and AUC24 values of 24.8 µg/mL, 0.25 h, and 270 µg*h/mL, respectively indicating that this dose produces 5-fold the single dose C_{max} in humans (of 4.3 µg/mL) or is equivalent to the C_{max} of 24 µg/mL at steady state.

Conditioned Place Preference

The Sponsor also conducted a conditioned place preference (CPP) study (Study # SK17004) which is used to determine if a drug can induce place conditioning which can be an indication of positive reinforcement. This study was designed to establish whether or not CDP could be used as a positive control in a future CPP study. CDP did not produce significant CPP in this study which is consistent with benzodiazepines producing weak reinforcement in this assay (Tzschentke, 2007). As a result, the Sponsor did not pursue the analysis of cenobamate using this assay.

Conclusion

The animal abuse-related studies indicate that cenobamate is weakly reinforcing at a dose of 0.0125 mg/kg/inj compared to vehicle but significantly lower than the positive control, midazolam, currently controlled in Schedule IV of the CSA. Furthermore, the drug discrimination studies indicate that rats, when tested at doses that produced therapeutic and supratherapeutic plasma levels in humans, partially generalized midazolam and fully generalized to CDP both in Schedule IV.

2.5 Tolerance and Physical Dependence Studies in Animals

The development of tolerance to repeated exposure of cenobamate was first tested in a mouse maximal electroshock seizure study (Study # pharm-nj-rg-13). In this study, male CF-1 mice were divided into two groups: group 1 received vehicle for 4 days and group 2 received 7.5 mg/kg IP of cenobamate for 4 days. On the fifth day all of the animals were given 7.5 mg/kg IP cenobamate and tested in the electroshock test for their seizure threshold defined as the abolition of hindlimb tonic extension. The dose was based on previously calculated ED_{50} values for seizure threshold. This study concluded that four of the eight vehicle treated animals did not have a seizure and three of eight animals did not have a seizure in the cenobamate treated animals. According to this study, the animals did not develop tolerance to cenobamate, however, a relatively low dose was used with dosing over 5 days. This study should have used higher doses over a longer period of time to develop conclusive results.

The Sponsor also conducted physical dependence studies in rats. Study # SK13024 was conducted in male Sprague Dawley rats who received oral cenobamate at 0, 6, 24, and 60 mg/kg/day or the positive control chlordiazepoxide at 3 mg/kg/day. Animals received drug for 14 days followed by a 7-day withdrawal phase during which no drug was administered. Animals were assessed for clinical observations, body weight, food consumption, body temperature and locomotor activity throughout the study. In accordance with the toxicity studies, the dosing phase of this study produced locomotor depression, decreased body weight, and decreased activity, however, no deaths were reported. The highest dose of 60 mg/kg/day for 14 days produced a C_{max} of 19.5 µg/mL and an AUC of 228 µg•hr/mL on day 14. This is similar to the C_{max} produced in humans of 24 µg/mL after 17 days of treatment with cenobamate at the therapeutic dose of 200 mg/day (Study # AA24143). Physical dependence should be tested at supratherapeutic doses and the Sponsor conducted Study # 14009 at 100 mg/kg/day to achieve the aforementioned supratherapeutic dose levels. In the physical dependence study, the results at the 60 mg/kg/day dose indicate that animals in the withdrawal phase had a trend towards decreased body weights (not significant), and decreased ambulatory and non-ambulatory levels (not significant). These effects were similar to the positive control chlordiazepoxide which did not yield significant withdrawal effects thereby invalidating the study.

Study # 14009 was conducted to increase the dose of cenobamate utilized in the assessment of physical dependence. Similar to the previous study, male Sprague Dawley rats received oral cenobamate at 0, 60, or 100 mg/kg/day or the positive control chlordiazepoxide at 50 mg/kg/day (as opposed to 3 mg/kg/day in study SK13024). According to the toxicity studies listed in **Table 11**, this is highest dose that rats can safely be maintained on daily dosing without detrimental effects. Animals received drug for 14 days followed by a 7-day withdrawal phase during which no drug was administered. Animals were then assessed for clinical observations, body weight, food consumption, body temperature and locomotor activity throughout the study. Cenobamate at a dose of 100 mg/kg/day for 14 days produced a Cmax of 37.6 µg/mL and an AUC of 438 µg•hr/mL, approximately twice that seen in humans at the therapeutic dose of 200 mg/kg. In this study, chlordiazepoxide (50 mg/kg) produced significant increases in body weight and food consumption, with decreases in activity and body temperature. For cenobamate, there were no significant alterations in the withdrawal phase of the study in the measured parameters at either of the tested doses. Both of the studies indicate that cenobamate does not have significant physical dependence in animals at the doses tested.

3. Clinical Pharmacology

Determining the clinical pharmacology of a drug is an important aspect in understanding the mechanism of action of a drug of abuse. Understanding the PK parameters can give an indication as to how a drug will be abused and therefore how it should be tested in a human abuse potential study.

3. 1 Absorption, Distribution, Metabolism, Elimination (ADME)

Absorption

The PK parameters of cenobamate were first determined in fasted humans in Study # AA22780 which was a phase 1 single ascending dose (SAD) study. Healthy male subjects were given single oral doses of cenobamate starting at 5 mg and doses were increased up to 750 mg. In this study, similar to the animal studies, the C_{max}, AUC, and half-life of cenobamate increased dose dependently. The clearance and volume of distribution of the drug were maintained across the dosing regimen and indicate that cenobamate distributes evenly throughout the total body water compartment. The highest proposed therapeutic dose of cenobamate, 400 mg, produced a C_{max} of 10.3 µg/mL, a t_{max} of 4 hours, an AUC of 750 µg*hr/mL, and a half-life of 59.8 hours (**Table 11**). These data indicate that the drug has a very long half-life and may be subject to accumulation over time, depending on the dosing regimen.

Table 11: PK Parameters of Single Oral Doses of Cenobamate in Healthy Adult Male Subjects (NDA 212839; Module 5.3.3.1; Study # AA22780, Table 11.4.7.1)

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

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

The Sponsor also conducted a study to determine the effect of food on the PK parameters of cenobamate. Study # AA39450 was an open label, randomized, single dose, 2-way crossover study in which 16 healthy male and female (11 and 5 respectively) subjects were orally administered 300 mg of

cenobamate in a fed or a fasted state. The data in **Table 12** demonstrate that the fed state decreases the C_{max} and overall exposure of the drug, while increasing the t_{max} and half-life. However, an oral dose of 300 mg in the fed state does not significantly affect the pharmacokinetics of cenobamate compared to the fasted state.

Table 12: PK Parameters of Cenobamate in Fed vs. Fasted State

Single administration	Fasted	Fed
Dose	300 mg	300 mg
C_{max} (µg/mL)	8.17 (1.41)	7.81 (1.30)
t_{max} (h)	3.56 (0.9)	4.50 (1.23)
AUC_t (µg*h/mL)	599 (124)	585 (128)
$t_{1/2}$ (h)	59.6 (19)	62 (20.3)

Data presented as arithmetic mean ± SD

The Sponsor also performed a PK comparison between male and female subjects given single and multiple oral doses of cenobamate in order to determine if sex differences were present. Female rats had a greater exposure and half-life than their male counterparts at higher doses (**Table 7**). To determine if this was the case in human subjects, 35 healthy subjects were fasted and given oral doses of cenobamate (150 mg) and the PK of the drug was assessed on day one and after 14 days of once a day administration (Study # AA24143). The dose of 150 mg is lower than the highest therapeutic dose of 400 mg, however, the results, in **Table 13** indicate that there are no significant sex differences in PK parameters after single oral administration, or after the drug has reached steady state (14-days). The data indicate that the drug accumulates over time with an accumulation index of approximately 5.

Table 13: PK Parameters in Male vs. Female Subjects after Day 1 and Day 14

Single administration	Oral			
Dose	150 mg - Day1		150 mg - Day 14	
	M	F	M	F
C_{max} (µg/mL)[a]	3.89 (17.5)	4.4 (10.9)	18.4 (10.7)	18.7 (19.1)
t_{max} (h)[b]	3 (1.00, 3.50)	2.5 (0.75, 8.00)	3 (1.00, 4.00)	2.06 (2.00, 3.50)
AUC_t (µg*h/mL) [a]	70.3 (19.2)	73.0 (15.0)	367 (9.99)	357 (19.5)
Accumulation index [a]	-	-	5.24 (11.4)	4.91 (9.1)

[a] data presented as arithmetic mean (%CV)
[b] median (minimum, maximum)

Distribution and Metabolism

In vitro plasma protein binding Study # Metab 2004-01 indicated that cenobamate has moderate plasma protein binding that is independent of dose ranging from 57.6% to 61.0% over a dose range of 0.114 µg/mL to 11.4 µg/mL.

The distribution and metabolism of cenobamate in humans was assessed using a mass balance study (Study # AA41857) in which ^{14}C-cenobmate at 50 μCi/400 mg was orally administered to fasted subjects. This study was an open-label single dose study in which cereal blood samples were collected up to 312 hours post dose for analysis of cenobamate and metabolite concentrations in the urine, feces, blood, and plasma. In this study, six adult males given 400 mg cenobamate produced a t_{max} of 1.5 hrs and a half-life of 81 hours. In plasma, 98% of the radioactivity was cenobamate and only the N-glucoronide metabolite (M1) was detected accounting for less than 2% of the radioactivity. Major metabolites are defined as being 10% of the concentration of the circulating parent compound. Since no major metabolites were detected in the plasma (circulating metabolites) the Sponsor was not required to conduct further studies assessing their effects.

The Sponsor did determine that cenobamate is heavily metabolized as only 6.8% of the parent drug is excreted. These studies determined that a total of ten metabolites were detected in the urine (M1, M2a, M2b, M3, M5, M6, M7, M11, P2, and P5) and six were detected in the feces (cenobamate, M1, M3, M6, M7, and M11).

Elimination

Study SK14002 and the above mass balance study determine that cenobamate is excreted mostly in the urine.

4. Clinical Studies

4.1 Human Abuse Potential Studies

1. Human abuse potential (HAP) study with cenobamate (Study # YKP3089C024)

This HAP study was a single-dose, randomized, double-blind, active- and placebo- controlled, double-dummy, 10-sequence, 5-way crossover study to determine the abuse potential of cenobamate relative to alprazolam and placebo in healthy, non-dependent recreational drug users with sedative drug use experience. The study consisted of four phases: screening, qualification, treatment, and follow-up.

Subjects were healthy male or female adults, 18 to 55 years of age who have used benzodiazepines for recreational purposes at least five times in the past year. A total of 53 subjects were randomized to the treatment phase and 39 subjects completed the study.

The inclusion and exclusion criteria are standard and include the following criteria that are of specific interest to an abuse-related study:

Inclusion criteria include:

- Current recreational drug users who have used benzodiazepines for recreational purposes (i.e., for psychoactive effects) at least 5 times in the past year and used benzodiazepines at least once in the 12 weeks before screening.

Exclusion criteria include:

- Substance or alcohol dependence (excluding caffeine or nicotine) within the past 2 years as defined by the DSM-IV-TR
- Participation in a substance or alcohol rehabilitation program to treat substance or alcohol dependence
- Heavy smoker (>20 cigarettes per day) and/or unable to abstain from smoking or unable to abstain from the use of prohibited nicotine-containing products for at least 10 hours.
- Use of prohibited medications or investigational drugs, including drugs associated with Drug Rash and Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Qualification Phase

The qualification phase consisted of a drug discrimination test in which subjects were asked to discriminate between the effects of the positive control, alprazolam (CIV), and placebo. Subjects were randomized to receive a single oral dose of 2.0 mg alprazolam (2 x 1.0 mg tablets) and placebo in a double-blind, crossover manner. Subjects were dosed on day 1 and day 2 of the study with each treatment being dosed approximately 24 hours apart. Subjects received the study drugs on test days following a fasting period of at least 8 hours. Subjects were required to continue fasting during the test session for at least 4 hours after treatment administration. The qualification criteria consisted of:

1. Peak score in response to 2.0 mg alprazolam greater than that of placebo on Drug Liking Visual Analog Scale (VAS) (difference of at least 15 points) and a score of at least 65 points for 2.0 mg alprazolam.
2. Acceptable placebo response based on Drug Liking (score between 40 and 60 points, inclusive).
3. Ability to complete the PD assessments and acceptable overall responses, as judged by the investigator or designee.
4. Able to tolerate 2.0 mg alprazolam as judged by the investigator or designee based on available safety data.
5. General behavior suggested that the subject could successfully complete the study, as judged by the research site staff.

Treatment Phase

The washout period between the last treatment of the Qualification phase and the first treatment of the Treatment phase was five days. Eligible subjects (as determined by the Qualification phase) entered the Treatment phase and remained as inpatients in the CRU. Subjects were randomized to receive each of the five treatments in a randomized, double-blind, double-dummy fashion:

- Placebo
- 1.5 mg alprazolam
- 3.0 mg alprazolam
- 200 mg cenobamate
- 400 mg cenobamate

The dose of cenobamate in this study was restricted to 400 mg by the Division of Neurology Products based on concerns that higher doses of the drug could lead to drug rash with eosinophilia and systemic symptoms (DRESS). Therefore, supratherapeutic doses of cenobamate were not tested in this study.

For each treatment, subjects were fasted for at least eight hours predose and for four hours post-dose. Study drug administration in each treatment period was separated by a minimum washout interval of 16 days because of the long half-life of cenobamate (~60 hours). Thus, a sufficiently long washout period was used in this study.

Subjective and Cognitive Measures

The T_{max} of alprazolam and cenobamate is 1-2 hours and 4 hours respectively. The assessment times varied depending on the endpoint to be measured, however, they covered the length of the study and PD assessments were conducted at the appropriate times. The pharmacodynamic measuresinclude the use VASs and the Addiction Research Center Inventory (ARCI) scales, safety endpoints, and the observer's assessments, and were conducted at predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24 hours postdose. All other assessments for PK and ARCI scales were conducted predose and 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

The primary measure was:

- Drug Liking VAS Emax (Bipolar)

The secondary measures included:

- Drug Liking VAS ("at this moment"), (Emin, TEmax, TEmin, TA_AUE)
- Overall Drug Liking VAS (Emax and Emin)
- Take Drug Again VAS (Emax and Emin)
- High VAS (Emax and Emin)
- Good Drug Effects VAS (Emax, TEmax, TA_AUE)
- ARCI MBG scale (Emax, TEmax, TA_AUE)
- Bad Drug Effects VAS (Emax, TEmax, TA_AUE)
- ARCI LSD scale (Emax, TEmax, TA_AUE)
- ARCI PCAG scale (Emax, TEmax, TA_AUE)
- Drowsiness/Alertness VAS (Emax, Emin, TEmax, TA_AUE)
- Any effects VAS (Emax, TEmax, TA_AUE)
- Relaxation/Agitation VAS (Emax, Emin, TEmax, TA_AUE)
- Dizziness VAS (Emax, TEmax, TA_AUE)
- Feeling Drunk VAS (Emax, TEmax, TA_AUE)

The Sponsor also assessed observer-rated measures of sedation and cognitive/psychomotor impairment:

- Observer assessment of alertness/sedation (OAA/S) scale
- Choice reaction time (CRT)
- Divided attention test (DAT)
- Sternberg short-term memory (SSTM) task

Pharmacokinetic Endpoints:

- C_{max}
- T_{max}
- AUC_{0-t}
- Half-life

Safety Endpoints:

- Incidence, frequency and severity of AEs
- Vital signs (blood pressure, respiratory rate, heart rate, and oral temperature)
- Electrocardiograms (ECGs)
- Clinical laboratory test results (clinical chemistry, hematology, urinalysis)
- Physical examination findings
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Results

Table 14 below depicts the effects of study treatments on subjective measures used in this study. The data below were drawn from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Ran Bi, FDA Office of Biostatistics (February 15, 2019). The primary measure of Drug Liking, as well as the secondary measures Take Drug Again, Overall Drug Liking, Good Drug Effects, High, Bad Drug Effects, and Any Drug Effects in response to cenobamate, alprazolam, and placebo were evaluated for statistically significant differences by Dr. Bi as well as the Sponsor. The data and statistical evaluation provided in Table 3 were produced by Dr. Bi. However, a statistical evaluation of the remaining secondary measures was conducted by Dr. Bi and by the Sponsor (see **Table 14**, below).

Subjects in the qualification phase had a maximum mean drug liking (bipolar VAS) score of 87.7 ± 10.9 when dosed with 2 mg of oral alprazolam. This is similar to the scores generated in the Treatment phase of the study using 1.5 mg and 3 mg of alprazolam generating scores of 79.5 $\pm$ 14.3 and 85.3 $\pm$ 13.5 respectively. The mean differences of these scores in the Treatment phase were statistically significantly greater than 15 points compared to placebo confirming the study validity.

Table 14: Effects of Oral Placebo, Alprazolam (1.5 and 3 mg), and Cenobamate (200 and 400 mg) on Key Subjective Measures (VAS) - Emax Scores (scale 0-100, mean and SD)

	Placebo	Alprazolam 1.5 mg	Alprazolam 3.0 mg	Cenobamate 200 mg	Cenobamate 400 mg
Drug Liking[A] (bipolar) (N=39)	52.3 ± 5.3	79.5 ± 14.3 *	85.3 ± 13.5 *	60.8 ± 14.6 ^	68.8 ± 16.5 *^
Take Drug Again[A] (bipolar) (N=34)	51.9 ± 5.9	84.3 ± 18.0 *	88.5 ± 15.9 *	61.5 ± 17.6 *^	70.4 ± 23.4 *^
Overall Drug Liking[A] (bipolar) (N=35)	52.2 ± 6.2	84.2 ± 15.4 *	88.2 ± 14.0 *	62.2 ± 16.1 ^	70.2 ± 18.4 *^
Good Drug Effects[A] (unipolar) (N=34)	0.7 ± 1.8	65.4 ± 25.8 *	78.6 ± 24.5 *	22.7 ± 30.7 *^	42.4 ± 37.3 *^
High[A] (unipolar) (N=33)	0.8 ± 2.3	65.4 ± 25.8 *	78.6 ± 24.5 *	22.7 ± 30.7 *^	42.4 ± 37.3 *^
Bad Drug Effects[B] (unipolar) (N=39)	0.4 ± 0.6	27.7 ± 32.3 *	32.1 ± 33.2 *	3.2 + 6.82 *^	8.4 ± 17.5 *^
Any Drug Effects[B] (unipolar) (N=39)	7.1 ± 16.3	66.4 ± 26.8 *	74.6 ± 22.48 *	20.4 ± 28.35 *^	38.5 ± 30.9 *^

[A] Data produced by Dr. Ran Bi in FDA Office of Biostatistics
[B] Data produced by Sponsor
* = $p < 0.05$ compared to placebo
^ = $p < 0.05$ compared to alprazolam

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an a priori defined acceptable placebo range of 40-60. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20.

At the primary endpoint, "Drug Liking (at the moment)," cenobamate 200 mg was not significantly different from placebo, however, cenobamate 400 mg was significantly higher than placebo and significantly lower than alprazolam (1.5 and 3 mg).

When Dr. Bi conducted her assessment of the secondary endpoints she noticed that several individuals within the study responded in a similar manner across all of the endpoints. Specifically, they responded near placebo across all of the endpoints, or they responded significantly higher than placebo across all of the timepoints. These responses may reduce the mean difference between placebo and the positive control (alprazolam), and placebo and the test drug (cenobamate). Dr. Bi conducted a sensitivity

analysis which removed these subjects from the analysis of the secondary endpoints leading to the different number of data points used in each assessment as seen in table 14. The change in the data resulting from the sensitivity analysis resulted in one change in the conclusion of the data from the original analysis. Specifically, the mean Take Drug Again E_{max} after 1.5 mg of alprazolam was statistically significantly greater than that of Cenobamate 400 mg.

Table 15 (below) shows the results of subjective measures that were evaluated by the Sponsor and not by the Office of Biostatistics. These include the Drowsiness/Alertness VAS, Relaxation/Agitation VAS, Dizziness VAS, Feeling Drunk VAS, and three Addiction Research Inventory (ARCI) measures: Morphine-Benzedrine Group (ARCI-MBG), Lysergic Acid Diethylamide (ARCI LSD), and the Pentobarbital, chlorpromazine, and alcohol group (ARCI PCAG). The data for all of the scales is presented as the mean (SD) of the Emax except for the Drowsiness/Alertness VAS and the Relaxation/Agitation VAS which present their respective Emin mean values. The data indicate that both the 1.5 mg and the 3.0 mg oral doses of alprazolam were significantly different than placebo, validating these scales. The 200 mg dose of cenobamate was significantly different from placebo on the ARCI PAG scale, Drowsiness/Alertness VAS, Relaxation/Agitation VAS, and the Feeling Drug VAS. The 400 mg dose of cenobamate was significantly different from placebo on all of the scales except the ARCI LSD scale. Furthermore, both the 200 mg and the 400 mg dose of cenobamate were significantly different from alprazolam on all of the secondary scales.

Table 15: Effects of Oral Placebo, Alprazolam (1.5 and 3 mg), and Cenobamate (200 and 400 mg) on Secondary Subjective Measures - E_{max} Scores (mean and SD) or E_{min} Scores (mean and SD)

	Placebo	Alprazolam 1.5 mg	Alprazolam 3.0 mg	Cenobamate 200 mg	Cenobamate 400 mg
ARCI MBG scale[#] (N=39)	1.6 ± 0.36	8.0 ± 0.8 *	9.1 ± 0.62 *	2.1 ± 0.53 ^	5.2 ± 0.79 *^
ARCI LSD scale[#] (N=39)	4.0 ± 0.12	5.8 ± 0.37 *	6.5 ± 0.32 *	4.2 ± 0.13 ^	4.4 ± 0.21 ^
ARCI PCAG scale[#] (N=39)	4.1 ± 0.31	10.0 ± 0.49 *	10.0 ± 0.45 *	5.3 ± 0.37 *^	7.1 ± 0.50 *^
Drowsiness/Alertness VAS (E_{min}) (bipolar) (N=39)	46.9 ± 1.24	14.6 ± 2.14 *	12.3 ± 2.35 *	34.8 ± 2.89 *^	30.7 ± 2.58 *^
Relaxation/Agitation VAS (E_{min}) (bipolar) (N=39)	45.3 ± 1.84	13.5 ± 2.02 *	11.5 ± 2.01 *	32.6 ± 2.93 *^	26.4 ± 2.73 *^
Dizziness VAS (unipolar) (N=39)	0.7 ± 0.26	34.5 ± 5.06 *	51.8 ± 5.18 *	3.4 + 2.56 ^	17.7 ± 4.65 *^
Feeling Drug VAS (unipolar) (N=39)	0.5 ± 0.13	27.7 ± 2.15 *	36.1 ± 4.87 *	3.4 ± 2.55 *^	12.0 ± 3.51 *^

[#] scale administered as a true/false questionnaire
* significantly different from placebo; $p < 0.05$
^ significantly different from alprazolam; $p < 0.05$

Pharmacokinetics

Table 16 presents the pharmacokinetic parameters measured in the HAP study after a single oral dose of 200 mg or 400 mg cenobamate. The PK parameters are consistent with those seen in the phase 1 and phase 2 studies.

Table 16: PK Parameters of a Single Dose of Oral Cenobamate at 200 or 400 mg in HAP Study # YKP3089C024

Dose (mg)	200	400
C_{max} (µg/mL)	5.61 (1.2)	10.9 (2.1)
t_{max} (h)	1.92	1.92
AUC_{last} (µg*h/mL)	94.6 (17.4)	197.6 (34.3)

Adverse events in HAP Study # YKP3089C024

The incidence of treatment emergent adverse events is captured in **Table 17**. According to this table cenobamate produces an increase in adverse events in a dose dependent manner. The highest therapeutic dose of 400 mg produced somnolence 19 (43.2%) and euphoric mood 8 (18.2%) in a large number of subjects.

Table 17: Summary of Abuse Related Treatment Emergent Adverse Events Occurring in HAP Study # YKP3089C024 – number of events (%)

Adverse Event Preferred Term	Placebo (N=45)	Alprazolam 1.5 mg (N=46)	Alprazolam 3.0 mg (N=46)	Cenobamate 200 mg (N=47)	Cenobamate 400 mg (N=44)
Somnolence	5 (11.1)	36 (78.3)	44 (95.7)	15 (31.9)	19 (43.2)
Headache	4 (8.9)	5 (10.9)	1 (2.2)	7 (14.9)	7 (15.9)
Dizziness	1 (2.2)	7 (15.2)	5 (10.9)	4 (8.5)	4 (9.1)
Feeling of relaxation	1 (2.2)	7 (15.2)	7 (15.2)	5 (10.6)	7 (15.9)
Feeling drunk	1 (2.2)	0	1 (2.2)	1 (2.1)	3 (6.8)
Euphoric mood	1 (2.2)	9 (19.6)	8 (17.4)	0	8 (18.2)

Overall Conclusions of HAP Study #YKP3089C024

The results of the HAP study show that:

- Alprazolam (1.5 and 3 mg)
    - Produced statistically significant increases in positive subjective measures compared to placebo, as would be expected from a Schedule IV benzodiazepine. This validates the study.
    - Produced depressant-like AEs
    - Was identified as a depressant in a drug similarity measure

- Cenobamate (200 mg and 400 mg)

- Produced statistically significant increases in positive subjective measures compared to placebo
  - Not to the same extent as the positive control (i.e., decrease relative to alprazolam)
- Produced meaningful abuse related adverse events
- Was identified as a depressant in a drug similarity measure
  - Not to the same extent as positive control

As a result, the data indicate that the highest therapeutic dose of cenobamate (400 mg oral) produced signals in experimental measures suggesting that the drug has abuse potential greater than placebo and less than alprazolam (CIV).

4.2 Adverse Event Profile Through all Phases of Development

The Sponsor conducted 21 Phase 1 Studies and 4 Phase 2/3 studies during the clinical development program for cenobamate. All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description of and analysis of abuse-related AEs found during different phases of clinical development.

Phase1 studies:
Single dose studies in healthy volunteers and those with liver or renal impairment: **Table 18** shows the abuse-related AEs in these studies

Table 18: Abuse related AEs in single dose studies in healthy subjects or those with liver or renal impairment

Study	N	Dose	Adverse events n (%)
AA39450	16	300 mg	Somnolence 6 (38)
YKP3089C019	14	100mg	none
YKP3089C032	60	100-200 mg	none
AA41857	6	400 mg	none
YKP3089C027	24	200 mg	none
YKP3089C028	31	200 mg	Somnolence 1 (3.2)
YKP3089C030	26	200 mg	none

Drug-drug interaction studies: Since anticonvulsant drugs are commonly co-prescribed with other drugs, the Sponsor conducted drug-drug interaction (DDI) studies. **Table 19** shows the abuse-related AEs in these studies.

Table 19: Abuse-related AEs in drug-drug interaction studies

Study	Cenobamate dose	N	Test drug	Adverse events n(%)
YKP3089C006	100 mg	28	Oral contraceptives	none

YKP3089C010	50 mg	16	Valproic acid	Somnolence 1(6.3)
YKP3089C011	200 mg	16	Carbamazepine	none
YKP3089C016	200 mg	16	Phenytoin	Feeling jittery 1 (6.2) Disturbance in attention 1 (6.2) Lethargy 1 (6.2) Somnolence 6 (37.5) Euphoric mood 1 (6.2)
YKP3089C022	50-200 mg	16	Phenobarbital	none
YKP3089C026	12.5-200 mg	21-24	Cytochrome P450 (CYP) probe drugs	Somnolence 5/24 (20.8) Mood altered 1/21 (4.8)
YKP3089C014	200 mg	15	Carbamazepine	Somnolence 1 (6.7) Euphoric mood 3 (20)

Study YKP3089C029: This was a single dose (YKP3089 200mg), crossover interaction study with alcohol in 32 healthy subjects. No abuse-related AEs were reported.

Single ascending dose studies: **Table 20** shows the abuse-related AEs in these studies with healthy subjects.

Table 20: Abuse-related AEs in single ascending dose studies

Study	Cenobamate dose	N	Adverse events n (%)
AA22780	5mg-750mg	7	Somnolence (750mg group) 4 (57.1)
YKP3089C031	50mg-400mg	24	none

Multiple Ascending dose studies (AA24143, YKP3089C009, YKP3089C018, YKP3089C020): **Table 21** shows the abuse-related AEs in these studies with healthy subjects (Cenobamate doses 50mg-600mg).

Table 21: Abuse-related AEs in multiple ascending dose studies n(%)

	Cenobamate N=124	Placebo N=84
Energy increased	1 (0.8) 300mg dose	
Psychomotor hyperactivity	1 (0.8) 300mg dose	

Somnolence	59 (47.6)	8 (9.5)
Feeling drunk	4 (3.2) 500mg and 600mg doses	
Feeling jittery	1 (0.8) 500mg dose	
Disturbance in attention	6 (4.8) 600mg dose	
Euphoric mood	4 (3.2) 500 mg and 600mg doses	
Mental status change	1 (0.8)	
Tachyphrenia	1 (0.8)	
Feeling abnormal	3 (2.4) 500mg dose	1 (1.2)
Abnormal behavior	2 (1.6) 500mg dose	
Mania	1 (0.8) 500 mg dose	
Decreased memory	2 (1.6)	

Conclusions Phase 1 studies: In single dose and single ascending dose studies, somnolence was the only abuse-related AE observed. The DDI studies showed an increase in euphoric mood with a combination of cenobamate and other anticonvulsants. Multiple ascending dose studies showed rates of euphoria and feeling drunk of about 3% and disturbance in attention of about 5% in subjects treated with cenobamate but these AEs were absent in the placebo group. Abuse-related AEs occurred at high therapeutic and supratherapeutic doses. Somnolence was present in cenobamate treated subjects but, in isolation, is not considered an abuse-related AE.

Phase 2 and 3 studies:

Pharmacodynamic Evaluation of YKP3089 in Epilepsy Patients with a Photo-induced Paroxysmal EEG-Response: Proof of Principle Phase 2a Protocol AA40616.
The aim of this study was to evaluate the onset and duration of the pharmacodynamic (PD) effect of YKP3089 in patients with epilepsy. This was a single blind, single dose, multi-center study in photosensitive epileptic patients. Patient participation lasted 1 to 72 weeks. Patients received doses of 100 mg-400 mg cenobamate. Overall, seven unique patients were enrolled and received at least one dose of study drug. Somnolence occurred in about 43% of patients treated with cenobamate

A Phase 2, multicenter, double-blind, randomized, adjunctive placebo-controlled trial with an open-label extension to evaluate the efficacy and safety of YKP3089in subjects with treatment resistant partial onset seizures Phase2 Protocol YKP3089C013
The primary objective of this study was to evaluate the efficacy of YKP3089 when titrated from 50 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 antiepileptic drugs (AEDs).

This was a multicenter, double-blind, randomized, placebo-controlled study, with an 8-week baseline period, a 12-week double-blind treatment period followed by a 1-week taper, and a 3-week follow-up period. Subjects who met all inclusion and exclusion criteria first underwent an 8-week baseline period to assess seizure frequency. Subjects who experienced at least 3 seizures/28 days during the baseline period were randomized in a 1:1 ratio to add-on placebo or YKP3089 given once per day in the morning. Subjects then entered a 12-week double-blind treatment period, consisting of a 6-week titration

phase and 6-week maintenance phase. The target dose for all YKP3089 treated subjects was 200 mg per day. During the titration phase, YKP3089 was dosed at 50 mg or placebo for the first 2 weeks and if well-tolerated the dose was increased gradually to 200 mg/day or placebo for the final 6-week maintenance phase. Following completion of the double-blind treatment period, YKP3089 was tapered down for 1 week and then discontinued. A follow-up visit occurred 21 days after discontinuation of the study medication. Subjects who completed the double-blind treatment period had the option to continue treatment in an open-label extension.

A total of 285 subjects were screened; 222 were randomized, 113 into the YKP3089 group and 109 into the placebo group. The median exposure in both treatment groups was 91 days with a range of 1 to 137 days in the YKP3089 group and 2 to 113 days in the placebo group.

Table 22 displays the abuse-related AEs in study YKP3089C013

Table 22: Abuse-related AEs YKP3089C013 n (%)

	YKP3089 N=113	YKP3089 50 mg N=112	YKP3089 100 mg N=104	YKP3089 150 mg N=96	YKP3089 200 mg N=71	Placebo N=109
Irritability	4 (3.5)	3 (2.7)	1 (0.96)	1 (1.04)	0	2 (1.8)
Disturbance in attention	2 (1.8)	0	0	2 (2.1)	0	0
Hypersomnia	1 (0.9)	1 (0.9)	0	0	0	1 (0.9)
Lethargy	1 (0.9)	1 (0.9)	0	0	0	1 (0.9)
Memory impairment	1 (0.9)	0	0	1 (1.04)	0	0
Mental impairment	1 (0.9)	1 (0.9)	0	0	0	0
Somnolence	25 (22.1)	10 (8.9)	11 (10.6)	8 (8.3)	6 (8.5)	13 (11.9)
Aggression	1 (0.9)	0	1 (0.96)	0	0	0
Anxiety	1(0.9)	1 (0.9)	0	0	0	6 (5.5)
Confusional state	4 (3.5)	2 (1.8)	0	1 (1.04)	1 (1.4)	0
Mood altered	1 (0.9)	0	0	0	1 (1.4)	0
Mood swings	2 (1.8)	1 (0.9)	0	1 (1.04)	0	1 (0.9)
Nervousness	2 (1.8)	0	1(0.96)	1 (1.04)	0	0

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Trial of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures, with Optional Open-Label Extension. Phase 2 ProtocolYKP3089C017

The primary objective of this study was to determine the effective dose range of YKP3089 as adjunctive therapy for the treatment of partial seizures. The study also evaluated the safety and tolerability of YKP3089 in the partial epilepsy population.

This was a multicenter, double-blind, randomized, placebo-controlled dose-response study in subjects with partial onset seizures. There was 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 2-week blinded 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. During the 8-week baseline period, subjects were to have had at least 8 seizures. Subjects with a high enough seizure frequency were randomly assigned in a 1:1:1:1 ratio to placebo or YKP3089 at 100 mg/day, 200 mg/day, or 400 mg/day for the 6-week titration phase. Subjects then entered a 12-week double-blind maintenance phase at their randomized dose level. Subjects who completed the double-blind maintenance phase were given the option to enter an open-label extension. Those not entering the open-label extension or who withdrew prematurely were tapered off the study drug over 3 weeks, followed by a final visit 14 days after the last dose of study drug. A total of 437 subjects were randomized at 107 study sites. **Table 23** shows the abuse-related AEs in YKP3089CO17.

Table 23: Abuse-related AEs Cenobamate n(%)

	Cenobamate 100mg N=108	Cenobamate 200mg N=110	Cenobamate 400mg N=111	Cenobamate N=108
Feeling abnormal	0	1 (0.9)	0	0
Amnesia	0	1 (0.9)	1 (0.9)	0
Cognitive disorder	0	1 (0.9)	0	0
Disturbance in attention	0	1 (0.9)	1 (0.9)	1 (0.9)
Hypersomnia	0	1 (0.9)	0	0
Memory impairment	2 (1.9)	3 (2.7)	2 (1.8)	1 (0.9)
Mental impairment	0	0	1 (0.9)	0
Sedation	1 (0.9)	2 (1.8)	2 (1.8)	0
Somnolence	20 (18.5)	23 (20.9)	41 (36.9)	9 (8.3)
Affect lability	0	0	1 (0.9)	0
Aggression	0	1 (0.9)	0	1 (0.9)
Agitation	0	0	1 (0.9)	0
Anxiety	2 (1.9)	2 (1.8)	3 (2.7)	1 (0.9)
Apathy	1 (0.9)	0	1 (0.9)	0
Bradyphrenia	0	0	1 (0.9)	0
Confusional state	2 (1.9)	2 (1.8)	3 (2.7)	0
Delirium	1 (0.9)	0	0	0
Depression	0	1 (0.9)	2 (1.8)	2 (1.9)
Disorientation	0	0	0	2 (1.9)
Euphoric mood	0	0	2 (1.8)	0
Hallucination visual	0	0	1 (0.9)	0
Irritability	1 (0.9)	1 (0.9)	2 (1.8)	0
Mood swings	0	0	1 (0.9)	0

Suicidal ideation	2 (1.9)	1 (0.9)	0	0
Suicide attempt	1 (0.9)	0	0	0

An Open Label, Multicenter, Safety and Pharmacokinetic Study of YKP3089 as Adjunctive Therapy in Subjects with Partial Onset Seizures Phase 3 Protocol YKP3089C021

The objective of this study was 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. The evaluations included:

1. Phenytoin-YKP3089 interaction
2. Phenobarbital-YKP3089 interaction
3. Long-term safety of YKP3089 as adjunctive therapy in subjects with partial onset seizures

This 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.

Subjects were supplied with YKP3089 12.5 mg, 25 mg, 50 mg, and 100 mg tablets to be taken orally once daily. After reaching the target dose of 200 mg/day, subjects were allowed to titrate up at 50 mg/day every other week to a maximum dose of 400 mg/day of YKP3089. **This study is of limited value in assessing abuse-related AEs as there was no placebo group and YKP3089 was administered along with other anticonvulsants which have CNS effects. Table 24** displays the abuse-related AEs in study YKP3089C021.

Table 24: Abuse-related AEs YKP3089C021 n (%)

	YKP3089 with concomitant antiepileptic drugs (N=1339)
Abnormal behavior	1 (0.07)
Accidental overdose	1 (0.07)
Affect lability	6 (0.45)
Aggression	11 (0.82)
Agitation	5 (0.37)
Amnesia	7 (0.52)
Anger	5 (0.37)
Anxiety	31 (2.32)
Bradyphrenia	9 (0.67)
Cognitive disorder	12 (0.90)
Confusional state	16 (1.19)
Delusion	2 (0.15)
Depressed mood	12 (0.90)
Depression	26 (1.94)
Disorientation	3 (0.22)
Disturbance in attention	17 (1.27)

Drug withdrawal syndrome	1 (0.07)
Dysphoria	2 (0.15)
Emotional disorder	1 (0.07)
Euphoric mood	2 (0.15)
Feeling abnormal	4 (0.30)
Feeling drunk	3 (0.22)
Feeling jittery	1 (0.07)
Hallucination	3 (0.22)
Hallucination, auditory	1 (0.07)
Hyperhidrosis	7 (0.52)
Hypersomnia	5 (0.37)
Intentional overdose	1 (0.07)
Irritability	29 (2.17)
Lethargy	20 (1.49)
Memory impairment	16 (1.19)
Mental impairment	2 (0.15)
Mood altered	3 (0.22)
Mood swings	5 (0.37)
Overdose	2 (0.15)
Panic attack	7 (0.52)
Psychomotor hyperactivity	2 (0.15)
Sedation	5 (0.37)
Somnolence	376 (28.1)
Suicidal ideation	10 (0.75)
Suicide attempt	4 (0.30)

Conclusions Phase 2 and 3 studies: Study YKP3089C021 is of limited value in assessing abuse-related AEs as there was no placebo group and YKP3089 was administered along with other anticonvulsants which have CNS effects.

The pooled abuse-related AEs from studies YKP3089C013 and YKP3089CO17 are displayed in **Table 25.** All AEs except anxiety occur at a higher rate in YKP3089 treated subjects than placebo. With the exception of somnolence, which, in isolation, is not an abuse-related AE, other abuse related AEs occur at low rates in YKP3089 treated subjects (0.5-2.5%)

Table 25: Pooled abuse-related AEs YKP3089C013 and YKP3089CO17 n (%)

	YKP3089 N=442	Placebo N=217
Irritability	8 (1.8)	2 (0.9)
Disturbance in attention	4 (0.9)	1 (0.5)
Memory impairment	8 (1.8)	1 (0.5)
Somnolence	109 (24.7)	22 (10.1)
Anxiety	8 (1.8)	7 (3.2)
Confusional state	11 (2.5)	0

Mood swings	3 (0.7)	1 (0.5)
Sedation	5 (1.1)	0
Euphoric mood	2 (0.5) Both at 400mg dose	0

4.3 Safety Profile

Phase 1, multiple ascending dose studies, in healthy subjects, showed rates of euphoria and feeling drunk of about 3% and disturbance in attention in about 5% in subjects treated with cenobamate and these AEs were absent in the placebo group. Abuse-related AEs occurred at high therapeutic and supratherapeutic doses. In Phase 2 and 3 studies AEs occur at low rates in YKP3089 treated subjects (0.5-2.5%). These results indicate that abuse-related AEs occur at low rates in YKP3089 treated subjects but at rates greater than placebo

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

The Sponsor evaluated four main sources of data from clinical studies for potential overdoses and noncompliance with study drug or diversion, including AE searches, protocol deviation records, drug accountability records, and compliance records. Searches of discontinuations related to lack of compliance to study medication were also conducted.

There were no cases of overdose reported in the Phase 1 studies. In the Phase 2/3 studies, there were 7 cases of overdose or medication error that were reported as AEs. These cases were primarily related to medication errors (e.g., taking 2 tablets instead of 1 on one or more occasions), observed in both cenobamate and placebo groups and were not considered to be related to abuse, diversion, or drug-seeking behavior. There were no intentional overdoses of cenobamate. There was 1 intentional overdose reported in Study YKP3089C021 that was related to a suicide attempt due to extreme stress; however, the subject did not overdose on cenobamate, but on other medications. While some subjects were discontinued due to non-compliance with study drug administration, these were mainly related to underdosing. In all clinical studies of cenobamate, there were no reports of misuse, abuse, or diversion.

4.5 Tolerance and Physical Dependence Studies in Humans

The Sponsor evaluated the potential for physical dependence in humans based on all spontaneously reported AEs observed following discontinuation in clinical studies in which cenobamate was administered for a minimum of 14 days, and a comparison with on-treatment AEs was made. Based on a t½ of approximately 50 to 60 hours, a TEAE was defined as discontinuation-emergent if it had an onset of at least three days following the end of study drug administration and up to 14 days (or data cut-off date, whichever came first). On-treatment AEs were those occurring between the first dose and up to two days after the last dose.

The primary analysis of physical dependence potential was based on Phase 1 studies in which

healthy subjects were abruptly discontinued from cenobamate treatment with study YKP3089C020 (QTc study) considered to be the most pertinent based on the dose of cenobamate evaluated (500 mg with up-titration) and duration of exposure (63 days).

Discontinuation-emergent AEs (DEAEs) reported in Phase 2/3 studies were also analyzed for patients who were discontinued from study participation, and for whom treatment was abruptly discontinued or tapered; however, their value is limited because of the presence of concomitant medications, and because few patients were abruptly discontinued since this would precipitate seizure activity.

A summary of DEAEs occurring in ≥2 subjects in study YKP3089C020 is presented in **Table 26**. In this double-blind, placebo-controlled, QTc study, subjects were up-titrated to and maintained on cenobamate 500 mg for 63 days and then abruptly discontinued and followed for up to 14 days. DEAEs occurring on abrupt discontinuation of cenobamate included insomnia, decreased appetite and weight, and amnesia.

Adverse events that were only reported following abrupt discontinuation of cenobamate 500 mg/day in study YKP3089C020 were depressed mood, nervousness, suicidal ideation (single subject), bradyphrenia, nightmare, dysmenorrhea, joint dislocation, head discomfort, pain and nasal congestion.

The Sponsor states that the low rate of DEAEs is consistent with the long t½ of cenobamate (≥50 hours at doses ≥200 mg), which results in an auto-taper phenomenon when treatment is abruptly discontinued.

Table 26: Number (%) subjects with discontinuation emergent AEs occurring in at least 2 subjects YKP3089C020 (Derived from Sponsor's Table 26 Drug abuse potential assessment)

	Up-titration to Cenobamate 500 mg On treatment (N=54)	Up-titration to Cenobamate 500 mg Off treatment (N=50)	Placebo – B On treatment (N=27)	Placebo – B Off treatment (N=25)	Placebo – C On treatment (N=27)	Placebo - C Off treatment (N=27)
Insomnia	3 (5.6)	4 (8.0)	0	0	0	0
Decreased appetite	2 (3.7)	3 (6.0)	0	0	2 (7.4)	0
Weight decreased	1 (1.9)	3 (6)	0	1 (4)	3 (11.1)	0
Amnesia	0	2 (4)	0	0	0	1 (3.7)

In other Phase 1 studies in which cenobamate doses of 100 to 600 mg (with up-titration) were administered for at least 14 days and abruptly discontinued (Studies AA24143, AA92064, YKP3089C018, YKP3089C006, YKP3089C016, YKP3089C026), there were no DEAEs of insomnia, decreased appetite, or weight decreased. Two subjects reported DEAEs of feeling jittery and suicidal ideation, feeling of medication dependence One subject had been exposed to phenytoin 300 mg

alone for 14 days and phenytoin 300 mg+cenobamate 200 mg for 14 days. Tremor was reported in 2 subjects

Overall, there were very few DEAEs reported in double-blind studies in patients. The only AEs reported off-treatment with cenobamate in two or more patients were dizziness. The incidence of this was higher or similar while patients were on-treatment as compared with the incidence off-treatment. The lack of DEAEs in the Phase 2/3 studies is expected as the majority of subjects were tapered off the study drug.

In summary, cenobamate leads to a withdrawal syndrome characterized by insomnia, decreased appetite, depressed mood, tremor, and amnesia. The label recommends gradual withdrawal of the drug

5. Regulatory Issues and Assessment

Based on the preclinical data, the HAP study, the abuse-related AE profile in clinical studies, and the physical dependence studies, we recommend that cenobamate be placed in Schedule V of the CSA.

CSS recommendations regarding the label are addressed in the Recommendations section.

III. REFERENCES

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DOMINIC CHIAPPERINO
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Signing also for Dr. Shalini Bansil.

Clinical Inspection Summary

Date	10/2/2019
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	LaShawn Dianat, Regulatory Project Manager Steven Dinsmore, M.D., Medical Officer Division of Neurology Products
NDA #	(b) (4)
Applicant	SK Life Science, Inc.
Drug	Cenobamate
NME	Yes
Proposed Indication	Treatment of Partial Onset Seizures
Consultation Request Date	1/28/2019
Summary Goal Date	9/20/2019, extended to 10/4/2019
Action Goal Date	11/21/2019
PDUFA Date	11/21/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Krauss, Sperling, and Varadarajulu were inspected as well as the sponsor, SK Life Science, and the clinical research organization (CRO), (b) (4) in support of this NDA. These inspections covered Protocols YKP3089C013 and YKP3089C017. Although inspectional observations were noted at one of the clinical investigator sites as well as at the sponsor and CRO, these findings are unlikely to have a significant impact on overall study results. The study data generated are considered acceptable and may be used in support of this NDA.

Significant seizure diary data discrepancies were noted in two subjects enrolled in Protocol YKP3089C017 at one site (Krauss). The seizure diary 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 review division should consider performing efficacy analyses based on these corrected seizure counts.

In the NDA submission, the sponsor had indicated that the double-blind database for Protocol YKP3089C017 had been unlocked on four separate occasions after the database hard lock date. The sponsor and CRO inspections were conducted, in part, 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 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 (duplicate entry). 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. This information was shared with the review division.

II. BACKGROUND

Cenobamate (YKP3089) capsules are being developed by SK Life Science, Inc., under NDA 212839 (IND 76809), for the treatment of partial onset seizures in adults. The sponsor has submitted the results of two Phase 2 studies, Protocols YKP3089C013 and YKP3089C017, to support the efficacy and safety of cenobamate in the treatment of partial onset seizures in adults.

Protocol YKP3089C013

Title: A Phase 2, multicenter, double-blind, randomized, adjunctive placebo-controlled trial with an open-label extension to evaluate the efficacy and safety of YKP3089 in subjects with treatment resistant partial onset seizures

Subjects: 222

Sites: 38 sites; U.S. (16), Asia/Pacific (15), and Eastern Europe (7)

Study Initiation and Completion Dates: 7/6/2011 to 6/15/2013

Data Cut-Off Date: 4/23/2018 (open-label extension is ongoing)

This was a randomized, double-blind, placebo-controlled study in subjects with partial onset seizures. Included were male or female subjects, 18 to 65 years of age, BMI between 18 and 40 kg/m^2, and a diagnosis of treatment resistant partial epilepsy.

The study consisted of five phases:
Baseline Phase (8 weeks): During this phase, subjects were to maintain a seizure diary. The diary was to be presented to study staff, approved by the sponsor/designee, and used for the 4-week retrospective baseline to be combined with a 4-week prospective baseline. Subjects who

experienced at least 3 seizures in 28 days during the baseline period with no 21-day seizure-free interval were randomized.

Treatment Phase (12 weeks): This period consisted of a 6-week titration phase and a 6-week maintenance phase. Subjects were randomized (1:1) to one of two study drugs, administered once daily, added to current antiepileptic drug (AED) therapy:

- Cenobamate capsules 50 mg x 2 weeks, 100 mg x 2 weeks, 150 mg x 2 weeks, 200 mg x 6 weeks; dose increases were based on tolerability
- Placebo capsules x 12 weeks

Taper Phase (1 week): Following completion of the treatment phase, study drug was tapered over a one-week period and then discontinued for subjects not continuing in the open-label extension phase.

Follow-up Phase (3 week): A follow-up visit occurred 3 weeks after the last dose of study drug.

Open-Label Extension Phase: Currently ongoing and to continue until development stopped by sponsor, product is approved for marketing, or at the discretion of the sponsor.

Subjects were given a paper diary to record seizures. The *primary efficacy endpoint* was the percent change in partial seizure frequency per 28 days during the double-blind period.

Protocol YKP3089C017

Title: A multicenter, double-blind, randomized, placebo-controlled, dose-response trial of YKP3089 as adjunctive therapy in subjects with partial onset seizures, with optional open-label extension (Phase 2)

Subjects: 437

Sites: 90 sites; U.S. (26), Eastern Europe (30), Western Europe (15), Asia/Pacific (7), Australia (6), and Middle East/Central Asia (6)

Study Initiation and Completion Dates: 7/31/2013 to 6/22/2015

Data Cut-Off Date: 4/23/2018 (open-label extension is ongoing)

This was a randomized, double-blind, placebo-controlled, dose-response study in subjects with partial onset seizures. Inclusion/exclusion were similar to Protocol YKP3089C013 with the following exceptions: 18 to 70 years of age (inclusive) and weigh $\geq$ 40 kg.

The study consisted of five phases:
Baseline Phase (8 weeks): Subjects had to experience $\geq$ 8 seizures during the baseline phase without a seizure-free interval > 25 days during the 8 weeks and at least 3 partial seizures during each of the 2 consecutive 4-week periods of the baseline phase to be eligible for randomization.

Treatment Phase (18 weeks): This period consisted of a 6-week titration phase and a 12-week maintenance phase. Subjects were randomized (1:1:1:1) to one of four study drugs, administered once daily, added to current AED therapy:

- Cenobamate 100 mg: initial dose of 50 mg/day, increasing by 50 mg/day/week increments to target dose
- Cenobamate 200 mg: initial dose of 50 mg/day, increasing by 50 mg/day/week increments to target dose
- Cenobamate 400 mg: initial dose of 50 mg/day, increasing by 50 mg/day/week to 200 mg/day, then increasing by 100 mg/day/week to target dose
- Placebo

Similar to Protocol YKP3029C013, this study included a Taper Phase (3 weeks), a Follow-up Phase (2 weeks), and an open-label Extension Phase.

Subjects were given a paper diary to record seizures. The *primary efficacy endpoint* was the percent change in seizure frequency per 28 days during the double-blind period compared to the baseline phase.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, and prior inspectional history. The site in India was chosen due to significant differences in efficacy between India and the United States.

III. RESULTS

1. Gregory Krauss, M.D.

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At this site for Protocol YKP3089C017 (Site #1016), 22 subjects were screened, 19 were randomized, and 18 subjects completed the double-blind phase of the study. Subject (b) (6) randomized to cenobamate 200 mg, discontinued the study due to the adverse event pruritic rash. Of note, Subject (b) (6), randomized to cenobamate 400 mg, completed the double-blind phase of the study on (b) (6) and died on (b) (6) (open-label phase). The death was reported as sudden unexpected death in epilepsy (SUDEP). The narrative for this death was included in the Integrated Safety Summary in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring

documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

Paper copies of seizure diaries were available at the site to verify against sponsor line listings. The FDA field investigator noted two instances of discrepancies as noted in Table 1. When asked about these discrepancies, the study coordinator stated that the eCRF did not allow entry of daily seizure counts >99 (greater than two digits). The data discrepancy for Subject (b) (6) was queried by the study monitor, but it is not known what further action was taken by the sponsor to address this issue.

Table 1. Discrepancies in Seizure Diary and Sponsor Data Listing for Seizure Counts

Subject	Treatment Arm	Date	Seizure* Count	
(b) (6)	Cenobamate 200 mg	(b) (6)	Seizure Diary	Sponsor Data Listing
			100 Type A 100 Type C	0 Type A 0 Type C
(b) (6)	Cenobamate 100 mg	(b) (6)	100 Type C	10 Type C

*Seizure types: Type A simple partial seizures without a motor/visual component; Type C complex partial seizures

There was no evidence of under-reporting of adverse events. Six SAEs occurred at this site, and all were reported to the sponsor as per protocol. Narratives are included in the NDA submission. All SAEs occurred during the open-label phase of the protocol:

- Death due to SUDEP as noted above (Subject (b) (6))
- Craniocerebral injury secondary to seizure/fall (Subject (b) (6))
- Colon cancer (Subject (b) (6))
- Psychomotor retardation and oral candidiasis (Subject (b) (6))
- Pulmonary embolism (Subject (b) (6))
- Seizure (Subject (b) (6))

Reviewer's comment: Since seizure counts >99 could not be entered in the eCRF system, an information request was sent to the sponsor to address this issue and to identify any other subjects with seizure counts >99 occurring in Protocol YKP3089C013 or YKP3089C017. The sponsor responded that the eCRF system for Protocol YKP3089C017 was designed to capture daily seizure counts to 2 digits primarily since there were no daily seizure counts >99 that occurred in Protocol YKP3089C013 and seizure counts >99/day were considered to be very rare for partial onset seizure patients.

The sponsor stated that for Protocol YKP3089C017, three data points of >99 seizures in three subjects were identified by review of seizure diaries and monitor/medical monitor queries. These included the two subjects as noted in Table 1 as well as Subject (b) (6) randomized to placebo, who experienced 121 Type B seizures (simple partial seizures with a motor component) on (b) (6) compared to 12 seizures per the sponsor data listing.

The review division should consider performing efficacy analyses based on the correct seizure counts in these 3 subjects' seizure diaries.

2. Michael Sperling, M.D.
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Philadelphia, PA 19107

At this site for Protocol YKP3089C013 (Site #110), 10 subjects were screened, 10 were randomized, and 9 subjects completed the double-blind phase of the study. Subject (b) (6) randomized to placebo, discontinued the study due to the adverse event status epilepticus.

For Protocol YKP3089C017 (Site #1010), 9 subjects were screened, 8 were enrolled, and 6 subjects completed the double-blind phase of the study. Two subjects discontinued the study due to noncompliance (Subject (b) (6) /cenobamate 400 mg) and serious adverse event (Subject (b) (6) /cenobamate 100 mg/suicidal ideation).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

Paper copies of seizure diaries were available at the site to verify against sponsor line listings. No data discrepancies were identified.

Seven SAEs occurred at this site for Protocols YKP3089C013 and YKP3089C017 (see below). The FDA field investigator reviewed site correspondence with the IRB, monitor, and/or sponsor for three of these SAEs (Subjects (b) (6)) which were found to be adequate. Narratives are included in the NDA submission.

<u>Protocol YKP3089C013</u>

- SUDEP during open label phase (Subject (b) (6))
- Status epilepticus (Subject (b) (6) /placebo). The blind was broken for this subject.
- Seizure during open label phase (Subject (b) (6)).
- Seizure during open label phase (Subject (b) (6))
- Death due to cardiac arrest during open label phase (Subject (b) (6))

<u>Protocol YKP3089C017</u>

- Suicidal ideation (Subject 1010001/cenobamate 100 mg)
- Epilepsy during open label phase (Subject (b) (6))

The FDA field investigator identified one instance of under-reporting of adverse events. Subject (b) (6) , enrolled in Protocol YKP3089C017 and randomized to cenobamate 400 mg, had recorded "felt toxic" in her paper seizure diary on (b) (6) and (b) (6) The progress notes do not mention this potential adverse event or clarify what the subject meant by "felt toxic". The only adverse events in sponsor data listings for this subject was dizziness occurring (b) (6)

A number of protocol deviations were noted for this site with regard to pregnancy testing, especially for Protocol YKP3089C013. For this protocol, serum pregnancy testing was required at screening/baseline (Visit 1), randomization (Visit 3), end of study (Visit 12), and follow-up (Visit 13). For all five female subjects enrolled in this protocol, pregnancy testing was not performed for at least one of these visits. For two of these subjects (b) (6) pregnancy testing was not performed during the screening/baseline visit (prior to randomization). This is of particular concern as the results of serum pregnancy testing at the randomization visit would not likely be available prior to actual randomization on that same day. For one of these subjects (b) (6), randomized to cenobamate, no pregnancy testing was performed until the follow-up visit (Visit 13). Of note, the results of all serum pregnancy tests performed were negative. The study monitor had noted these protocol deviations, but it is unclear what processes were put into place to address these deviations in real time. Similar deviations were not noted for Protocol YKP3089C017, which allowed for both urine and serum pregnancy testing.

Table 2. Protocol Deviations for Pregnancy Testing (Protocols YKP3089C013)

Subject Treatment group	Pregnancy Testing Obtained Per Protocol			
	Visit 1 (Screening/Baseline)	Visit 3 (Randomization)	Visit 12 (End of Study)	Visit 13 (Follow-up)
(b) (6) /cenobamate	No	Yes	No	No
(b) (6) /cenobamate	Yes	Yes	Yes	No
(b) (6) /placebo	Yes	No	Yes	No
(b) (6) /placebo	Yes	Yes	No	Yes
(b) (6) /cenobamate	No	No	No	Yes

Reviewer comments: Under-reporting of adverse events occurred in one of ten enrolled subjects for Protocol YKP3089C017. There was a lack of documentation that the adverse event, "felt toxic", experienced by a subject randomized to cenobamate 400 mg, was evaluated by the clinical investigator. This potential adverse event was not reported to the sponsor. Since there was a lack of follow-up, the correct terminology for this verbatim term is unclear.

The lack of pregnancy testing that occurred in Protocol YKP3089C013 posed a potential risk to those enrolled subjects. For one subject (b) (6), randomized to cenobamate, there was no pregnancy testing performed while taking study drug. For this subject and another (b) (6) pregnancy testing was not performed prior to randomization. The study monitor had communicated these deviations to the clinical investigator and they are included in sponsor data listings. Similar protocol deviations did not occur for subjects enrolled in Protocol YKP3089C017.

3. Reginald Varadarajulu, M.D.
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Bangalore, Karnataka 560043
India

For Protocol YKP3089C013 (Site #209), 15 subjects were screened, all of whom were enrolled and randomized, and 10 subjects completed the double-blind phase of the study. Five subjects discontinued the study due to "withdrawal by subject" (n = 2), "other" (n = 1), loss to follow-up (n = 1), and adverse event (n = 1). The discontinuation due to adverse event occurred in Subject (b) (6) randomized to cenobamate, who experienced the SAE of drug hypersensitivity one to three hours after taking the first dose. The narrative for this SAE was included in the NDA submission.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (seizures).

Paper copies of seizure diaries were available at the site to verify against sponsor line listings. Only one data discrepancy was identified. Seizure diaries for Subject (b) (6) randomized to placebo, recorded one seizure occurring on (b) (6) that was not entered into the eCRF and therefore not included in the data listings. The FDA field investigator did not indicate the type of seizure the subject experienced.

There was no evidence of under-reporting of adverse events. Three SAEs occurred at this site and were reported to the sponsor as per protocol.

- Status epilepticus during taper phase of protocol (Subject (b) (6) /cenobamate),
- Convulsion (Subject (b) (6) /placebo)
- Hypersensitivity as noted above (Subject (b) (6) /cenobamate)

Reviewer comments: A single seizure occurring in a subject randomized to placebo was not reported to the sponsor. It is unlikely that this omission would impact overall efficacy analyses.

4. SK Life Science, Inc.
22-10 Route 208 South
Fair Lawn, NJ 07410

This inspection covered sponsor practices related to Protocols YKP3089C013 and YKP3089C017. For Protocol YKP3089C013, the inspection focused on two clinical investigator (CI) sites that had been selected for inspection (#s 110, 209) as well as some additional CI sites (#s 111, 116). For Protocol YKP3089C017, the inspection focused on one

of the clinical investigator sites that had been selected for inspection (#1016) as well as some additional CI sites (#s 1005, 1029, 10004, 15004, and 16001).

Records reviewed included, but were not limited to, organizational charts, SOPs, monitoring plans and reports, transfer of responsibilities, contract agreements, selection of monitors and clinical investigators, correspondence, training, Form FDA 1572s, financial disclosure forms, audit trails, data management plans, quality assurance audits, electronic trail master files, protocol deviations, adverse event reporting/serious adverse events, and test article accountability.

Clinical monitoring was conducted by (b) (4) for Protocol YKP3089C013 and (b) (4) for Protocol YKP3089C017. There were no deficiencies identified with the clinical monitoring for these studies. No sites were terminated due to noncompliance during the conduct of either study.

In the Clinical Study Reports (CSRs) for Protocols YKP3089C013 and YKP3089C017, the sponsor noted that the database had been unlocked after unblinding, with subsequent changes being made to the database. Issues of database locking and unlocking were therefore addressed during the sponsor inspection.

Database Lock/Unlock

Protocol YKP3089C013
The double-blind clinical database for Protocol YKP3089C013 was initially locked on 7/29/2013 and the study unblinded. The database lock memo obtained during the inspection noted that the database was locked with the understanding that the pharmacokinetic data reconciliation as well as outstanding queries for three subjects was pending. After pharmacokinetic data reconciliation and resolution of queries, the final database lock occurred on 10/16/2013. The sponsor provided audit trails for the time period from the first database lock (7/29/2013) to the final database lock (10/16/2013). Documentation of the final database lock date was available during the inspection, and this date was verified. During the inspection, a review of these audit trails did not identify any significant issues.

Reviewer comments: A review of the audit trails for Protocol YKP3089C013 did not identify any undisclosed changes to the database or changes to the seizure diary data.

Protocol YKP3089C017
There was one database that included both the double-blind phase as well as the ongoing, open-label phase of the study. The database for the double-blind phase of the study was hard locked on 7/7/2015, with the data subsequently being transferred to the statistical vendor, (b) (4) The study was unblinded on 7/8/2015.

In the CSR, the sponsor stated that the YKP3089C017 database was "formally unlocked and locked" four times following unblinding of the study in order to "improve the completeness of the database." According to the sponsor, these database unlocks and locks occurred on 11/6/2015, 12/14/2015, 1/8/2016, and 1/25/2016. In the 74-day (filing) letter, the review

division asked the sponsor to provide a list of all changes made during these database unlocks. In their response, the sponsor stated that they were informed of discrepancies post double-blind database lock and decided to unlock the database at four different time points so that "minor" changes could be made by the respective clinical investigator sites in order to resolve these discrepancies. The sponsor further stated that these database changes occurred in seven subjects and included changes to prior concomitant medications, concomitant antiepileptic drugs, medical history, visit dates, full and brief neurological examinations, eligibility criteria, and vital signs. The eligibility criteria change was a yes/no response field for one subject who met exclusion criterion 16 (concomitant medication). The sponsor did not indicate that any changes were made to the primary efficacy endpoint data (i.e., seizure diary data).

The CRO, (b) (4) was responsible for database locks and unlocks. (b) (4) SOPs required sponsor approval for modifications to study data. During the inspection, the sponsor provided all audit trails for the time period 7/7/2015 (database hard lock) to 2/3/2016 (estimated final database lock date). It was unclear if the database was ever "relocked" since no documentation was available indicating the sponsor's approval of a final database lock occurring after the database unlocks. Sponsor approval was in fact given for the four database unlocks as indicated above.

Of note, one database change was identified for seizure diary data (i.e., the primary efficacy endpoint data). Subject (b) (6) randomized to cenobamate 400 mg, experienced a seizure on the Visit 9/End of Study (EOS) visit (b) (6), but the seizure occurred later in the day, after the visit had been completed. This seizure had been entered into the database twice and, following unlock, was removed from the Visit 9 double-blind phase *(see reviewer comments below).* The sponsor had approved this database unlock on 11/6/2015 but did not disclose this change in the summary of database changes they had provided to the review division. The sponsor inspection found that although (b) (4) was responsible for the database locking and unlocking,

A preliminary review of the audit trails also noted that other subject records were unlocked after 7/7/2015 (hard lock date), on dates other than those disclosed by the sponsor (see CRO inspection summary below). SK Life Science did not ensure that (b) (4) was following their standard operating procedures for locking and unlocking the database. In their response to this inspectional finding, SK Life Science acknowledged that (b) (4) did not follow their SOP for locking and unlocking the database. To prevent a recurrence of this finding, SK Life Science will implement an SOP that describes procedures for reviewing and approving the locking, unlocking, and relocking of databases for all clinical studies.

Reviewer comments: Since there was no documentation of the final database lock date for Protocol YKP3089C017, the sponsor was asked, following the inspection, to provide a summary of changes to the double-blind database as well as the audit trails from 2/4/2016 to the time the NDA was submitted. The sponsor submitted this data on 9/11/2019. A review of these data, in addition to the audit trails requested during the inspection, was performed. Due to time constraints, the review was limited to seizure diary data (primary endpoint data) and adverse events. It was confirmed that the only change to seizure diary data was for Subject (b) (6) *as discussed above. In response to an additional information request, the sponsor confirmed that the database was unlocked on 11/10/2015 to update subject records including*

to inactivate a duplicate seizure record for Subject (b) (6) as discussed above.

The end of study visit for the double-blind phase (Visit 9) for Protocol YKP3089C017 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. The sponsor commented that this was consistent with the Statistical Analysis Plan (SAP); however, in this reviewer's opinion, the SAP did not appear to be that specific. 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. The numbers of seizures occurring on the Visit 9 date in the placebo and cenobamate 200 groups were similar and were greater than in the cenobamate 100 and 400 mg groups. All things being equal, a Visit 9 imbalance showing higher seizure counts in the cenobamate groups compared to the placebo group would have favored cenobamate in the statistical analyses, as these seizures were not counted in the seizure counts for the double-bind phase. Since this imbalance was not present, it is unlikely that not counting seizures occurring on Day 9/EOS in the double-blind phase impacted the overall efficacy analyses. These data were shared with the review division.

Since (b) (4) was responsible for the database unlocks, and there appeared to be some database changes on dates other than those disclosed by the sponsor, an inspection of this CRO was conducted to further investigate this issue (see (b) (4) inspection summary below).

Database Corruption/Migration Issues

Protocol YKP3089C017
In the NDA submission, the sponsor had disclosed a database corruption issue for Protocol YKP3089C017. The double-blind database was transferred to (b) (4) the statistical vendor, in early February 2016. During (b) (4) review of the final tables and listings, it was discovered that the database was corrupted during the transfer from (b) (4) to (b) (4). (b) (4) conducted a data integrity audit of the database and concluded that data integrity was not compromised. The final database was transferred from (b) (4) to (b) (4) in September 2016.

During the inspection, the sponsor provided a summary of the data migration issue. Review of this information revealed that data for two subjects ((b) (6)/cenobamate 400 mg and (b) (6)/placebo) were lost during the migration. Once discovered, the data was restored. Corrective actions were taken to prevent recurrence of this data migration issue.

Reviewer comment: The database corruption issue was limited in scope and appropriate actions were taken by the sponsor to restore data.

Data Collection and Handling

Protocol YKP3089C017
Insufficient and inadequate validation were observed with (b) (4) interactive response technology (IRT) system that resulted in a number of protocol deviations and drug supply

issues at clinical trial sites. The sponsor did not conduct their own user acceptance testing (UAT) of the IRT system but participated as a user in the UAT that (b) (4) conducted.

- The interactive web response system (IWRS), a type of IRT system, allowed for two consecutive dose reductions to occur, which was not allowed per protocol. During the inspection, these protocol deviations were identified for at least four subjects (b) (6) and were included in the sponsor data listings.

- There was insufficient drug supply at seven clinical sites due to the IRT system not being fully validated. This issue is further discussed in the (b) (4) inspection summary below.

Reviewer comments: The two consecutive dose reduction issue may have been averted if the sponsor had conducted a UAT testing of the IWRS. (b) (4) *was responsible for the IWRS and further comments are included in the* (b) (4) *inspection summary.*

5. (b) (4)

This inspection covered (b) (4) monitoring activities of clinical sites participating in Protocol YKP3089C017, in particular the two clinical investigator sites that had been inspected (Sites 1010, 1016) for this protocol. The inspection also focused on the findings noted during the sponsor inspection (see above), including database locking and unlocking procedures, database corruption/data migration, and data collection and handling issues.

Records reviewed, but were not limited to, FDA 1572s, financial disclosure forms, training documentation for investigators/study staff/monitors, sponsor and internal correspondence, adverse reactions, safety reports, protocol deviations, transfer of regulatory obligations, master services agreement, IRT validation reports, SOPs, and corrective and preventive action (CAPA) plans.

For Protocol YKP3089C017, (b) (4) was responsible for project oversight, monitoring of sites, import/export of supplies, data management, pharmacovigilance, central lab services, electronic Trial Master File, interactive response technology (IRT), vendor contracting, investigator contracts, medical writing, and quality assurance. Records reviewed indicated that (b) (4) had maintained adequate oversight and monitoring of the clinical trial.

Database Lock/Unlock

Please refer to the Database Lock/Unlock in the sponsor inspection summary (above) for details.

The (b) (4) inspection was able to confirm that sponsor approval was given for database unlocks on the dates provided by the sponsor. The sponsor inspection identified a limited number of

additional database unlocks after database hard lock on dates other than those provided by the sponsor. (b) (4) responded that these additional unlocks were done in error, no data was changed, and the (b) (4) personnel were retrained.

Reviewer comments: This inspection confirmed that (b) (4) received sponsor approval for the four database unlock dates as stated in the clinical study report. There were a few instances of database unlocks without sponsor approval that were, according to (b) (4) unlocked in error and no changes were made. Upon the review of the audit trails, with a focus on the seizure diary and adverse event fields, the only significant change noted was the deletion of the duplicate seizure occurring in Subject (b) (6) as described in the sponsor inspection summary above.

Data Collection and Handling

Issues related to insufficient and inadequate validation were observed with (b) (4) interactive response technology (IRT) system that resulted in a number of protocol deviations and drug supply issues at clinical trial sites. Sufficient UAT was not conducted by either the sponsor or (b) (4)

- The interactive web response system (IWRS), a type of IRT system, allowed for two consecutive dose reductions to occur, which was not allowed per protocol. In addition to the four subjects identified during the sponsor inspection in which these deviations occurred, (b) (4) identified two additional subjects (Subjects (b) (6)) who received two consecutive dose reductions. The sponsor data listing does not include the protocol deviations for these two addition subjects. This IWRS issue was identified on 7/21/2014 and a corrective action plan was implemented.

- There was insufficient drug supply at seven clinical sites due to the IRT system not being fully validated. The drug shipments generated by the IWRS from approximately 5/8 – 5/19/2014 were not sent to (b) (4) (drug distribution vendor) in time for investigational product to be on-site. A back-up, manual process for drug dispensing was established until the issue could be resolved. The root cause indicated that the system was operating in an unvalidated state.

  In addition, study personnel did not follow the manual process correctly, and the same kit number was assigned at Visit 6 to subjects (b) (6) resulting in partial unblinding of treatment assignment for these two subjects. That is, study personnel were aware that these two subjects were randomized to the same treatment group. These subjects in fact were randomized to cenobamate 200 mg.

Reviewer comments: The two consecutive dose reductions involved five (4.5%) subjects randomized to cenobamate 400 mg and one (<1%) subject randomized to cenobamate 200 mg. According to (b) (4) *the IWRS issue wasn't identified until 7/2014, approximately one year after the first subject was enrolled. However, these protocol deviations occurred for a small number of subjects such that any impact on the overall study results is unlikely.*

The partial unblinding for two subjects due to errors in the manual drug dispensation process was not disclosed in the submission; however, there is no evidence that the blind was broken for these subjects. Since the primary efficacy endpoint was derived from seizure diaries completed by subjects, it is unlikely that this partial unblinding occurring in two subjects would impact the overall efficacy analyses.

{See appended electronic signature page}

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OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
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OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 23, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablet, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	SK Life Science, Inc.
OSE RCM #:	2018-2559-2
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader (Acting):	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 13, 2019 for Xcopri. The Division of Neurology Products (DNP) requested that we review the revised labels and labeling for Xcopri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and label and labeling memorandum.[ab] Our assessment, and corresponding recommendations, for Section 16 'How Supplied/Storage and Handling' of the Prescribing Information (PI) is also provided under this cover.

2 CONCLUSION & RECOMMENDATIONS

Our review of the revised container labels and carton labeling, and Section 16 of the PI identified the following areas of needed improvement that may contribute to medication errors:

[a] Rider B. Label and Labeling Review for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 APR 18. RCM No.: 2018-2559.
[b] Little C. Label and Labeling Memorandum for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 AUG 08. RCM No.: 2018-2559-1.

- We note that the placeholder, "TRADENAME" is included on the container labels and carton labeling. However, the proposed proprietary name, Xcopri, was found to be conditionally acceptable on February 11, 2019.[c]
- As currently stated on the inside of the titration blister packs (e.g., 12.5 mg WEEK 1), it is not immediately clear that the designated strength is per unit, which may lead to wrong dose errors.
- As currently presented, the 250 mg daily dose and 350 mg daily dose maintenance blister packs are not adequately differentiated, which may lead to selection errors.
- Section 16, How Supplied/Storage and Handling, of the prescribing information can be improved to include the dosage form, strength, NDC number, and tablet description for the 30-count bottle configuration, and the dosage form, daily dose, NDC number, supplied as (strength/quantity), and tablet description for the titration blister pack and maintenance blister pack configurations.

2.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
    1. How Supplied/Storage and Handling (Section 16)
        i. As currently presented, the dosage form (tablet) and tablet description is not included. Additionally, the expression of strength/quantity for the titration blister pack and maintenance blister pack configurations does not clearly convey the titration schedule or daily dose. We recommend Section 16.1 of the PI be revised for completeness and clarity. See Appendix B for our proposed revisions.

2.2 RECOMMENDATIONS FOR SK Life Science, Inc.

We recommend the following be implemented prior to approval of this NDA:

A. General Recommendations for the Container Labels and Carton Labeling
    1. The proprietary name is currently denoted by a placeholder, "TRADENAME". We reference our February 11, 2019 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Xcopri, was found conditionally acceptable. Replace the placeholder, "TRADENAME" with the conditionally acceptable proprietary name, Xcopri, on the container labels and carton labeling.

B. Titration Pack Carton Labeling (NDCs: 71699-201-28, 71699-202-28, and 71699-203-28)
    1. As currently stated on the inside of the titration blister packs (e.g., 12.5 mg WEEK 1, 12.5 mg WEEK 2, 25 mg WEEK 3, 25 mg WEEK 4), it is not immediately clear that the designated strength is per unit. We recommend you revise the strength statement on the inner labeling of the titration packs to make it clear

[c] Harris, D. Proprietary Name Request Conditionally Acceptable letter for Xcopri (NDA 212839). 2019 FEB 11. Available in DARRTS via: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804dae96&_afrRedirect=4976774472432786

that the designated strength is per unit (e.g., "X mg per tablet") so there is no confusion as to how much product is contained in a single unit, as compared to the total contents of the week. For example, consider revising to read:

WEEK 1 OR WEEK 1: 12.5 mg per tablet
12.5 mg per tablet

C. Maintenance Pack Carton Labeling (NDCs: 71699-102-56 and 71699-103-56)

1. As currently presented, the principal display panel (PDP) of the 250 mg daily dose and 350 mg daily dose maintenance blister packs are not adequately differentiated, which may lead to selection errors. (b) (4)

Revise the font colors (b) (4)

Ensure the colors do not overlap with any other colors utilized in highlighting the other product strengths or the proprietary name.

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APPENDIX B. PROPOSED REVISIONS TO SECTION 16.1 (HOW SUPPLIED) SECTION OF THE PRESCRIBING INFORMATION

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Xcopri tablets are supplied in the following configurations:

Bottles; 30 count

Strength	NDC Number	Tablet Description (Color, Shape, Markings)
50 mg	71699-050-30	Film coated round yellow tablets with SK on one side and 50 on the other side
100 mg	71699-100-30	Film coated round brown tablets with SK on one side and 100 on the other side
150 mg	71699-150-30	Film coated round light orange tablets with SK on one side and 150 on the other side
200 mg	71699-200-30	Film coated modified oval light orange tablets with SK on one side and 200 on the other side

Titration Blister Packs; 28-Day

Daily Dose	NDC Number	Supplied As (strength/quantity)	Tablet Description (Color, Shape, Markings)
12.5 mg per day for 14 days, then 25 mg per day for 14 days	71699-201-28	12.5 mg (14-count)	Uncoated round white to off-white tablets with SK on one side and 12 on the other side
		25 mg (14-count)	Film coated round brown tablets with SK on one side and 25 on the other side
50 mg per day for 14 days, then 100 mg per day for 14 days	71699-202-28	50 mg (14-count)	Film coated round yellow tablets with SK on one side and 50 on the other side
		100 mg (14-count)	Film coated round brown tablets with SK on one side and 100 on the other side
150 mg per day for 14 days, then 200	71699-203-28	150 mg (14-count)	Film coated round light orange tablets with SK on one side and 150 on the other side

mg per day for 14 days		200 mg (14-count)	Film coated modified oval light orange tablets with SK on one side and 200 on the other side

Maintenance Blister Packs; 28-Day

Daily Dose	NDC Number	Supplied As (strength/quantity)	Tablet Description (Color, Shape, Markings)
250 mg per day	71699-102-56	50 mg (28-count)	Film coated round yellow tablets with SK on one side and 50 on the other side
		200 mg (28-count)	Film coated modified oval light orange tablets with SK on one side and 200 on the other side
350 mg per day	71699-103-56	150 mg (28-count)	Film coated round light orange tablets with SK on one side and 150 on the other side
		200 mg (28-count)	Film coated modified oval light orange tablets with SK on one side and 200 on the other side

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/s/

CELESTE A KARPOW
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 8, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablets, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Applicant/Sponsor Name:	SK Life Science, Inc.
FDA Received Date:	May 9, 2019
OSE RCM #:	2018-2559-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader (Acting):	Briana Rider, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised labels and labeling received on May 9, 2019 for Xcopri. The Division of Neurology Products (DNP) requested that we review the revised labels and labeling for Xcopri (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised labels and labeling for Xcopri are unacceptable from a medication error perspective.

- The "recommended dosage" statement does not appear on the container labels.
- The established name and dosage form are not clearly separated from the proprietary name on container labels.
- The net quantity statement is located in close proximity to the strength expression on the container labels for the maintenance packs and titration packs.

[a] Rider B. Label and Labeling Review for Xcopri (NDA 212839). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US);2019 APR 18. RCM No.: 2018-2559.

- The Principal Display Panel (PDP) on the titration pack container labels does not clearly indicate the dosing titration.
- On the PDP on the maintenance pack container labels, the strength expression and dosing information (i.e., (b) (4)) can be clarified.
- For the 12.5 mg and 25 mg Titration Pack, the strength is presented (b) (4) (b) (4)

We provide recommendations to address these concerns in Section 3 below.

3 RECOMMENDATIONS FOR SK LIFE SCIENCE, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (30-count bottles, Maintenance packs, Titration packs)
   1. The "recommended dosage" statement does not appear on the container labels. The "recommended dosage" statement is required per 21 CFR 201.55. Revise the statement (b) (4) to read "Recommended dosage: see prescribing information", or a similar statement.
   2. The established name (cenobamate) and dosage form (tablets) are not clearly separated from the proprietary name which is not in accordance with the Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013). We are concerned this lack of separation will decrease the readability and pose risk of medication error of product selection. We recommend you clearly separate the established name from the dosage form by use of parenthesis as follows: "(cenobamate) tablets". See example below:

      TRADENAME

      (cenobamate) tablets

B. Container Labels (Maintenance packs, Titration packs)
   1. The net quantity statement (e.g., "pack contains…") is located in close proximity to the strength expression (e.g., "250 mg"). From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.[b] Consider relocating the net quantity statement to the bottom of the primary display panel away from the strength expression.

C. Container Labels (Maintenance packs)
   1. We acknowledge that you have simplified the strength expression on the Primary Display Panel (PDP) in a manner that is consistent with the intended daily dose. However, as presented, we are concerned that end users may misinterpret the daily dose as the strength of each tablet, which could lead to

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

wrong dose medication errors. Therefore, we recommended revising the strength expression on the maintenance pack container labels to include the statement, "daily dose". For example, "350 mg daily dose".

2. We acknowledge the addition of the daily dosing instructions, (b) (4) , on the PDP. However, as currently presented, we are concerned that the daily dose instructions lack prominence and do not clearly state that two tablets of two different strengths are administered once daily to achieve the intended daily dose, which could lead to wrong dose medication errors. Revise the daily dosing instructions to read: "Take one XX mg tablet and one XX mg tablet once daily", or a similar statement. Additionally, we recommend increasing the prominence of the revised daily dosing instructions statement.

D. Container Labels (Titration packs)

1. The PDP of the titration pack configurations do not clearly convey the dosing titration, which could result in product selection and dispensing errors. We recommend revising the PDP of the titration pack container labels to clearly indicate the dosing titration. For example, add the statement "Take XX mg once daily for two weeks, followed by XX mg once daily for two weeks" to the PDP. Or, address this concern by other means.
2. For the 12.5 mg and 25 mg Titration Pack,
    i. each strength is not presented with a unit of measure on the PDP. Expressing the strength presentation without a unit of measure can lead to confusion and dosing errors. Revise the strength presentation to include the corresponding unit of measure of each numerical value. (i.e., "12.5 mg" and "25 mg").
    ii. we note that the strength presentatio (b) (4)

    Inconsistencies in strength presentation may lead to confusion. We recommend (b) (4)

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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212839
Submission Number	001
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Clinical Division	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 76806 dated 07/09/2014; 02/19/2015; 04/27/2015 in DARRTS;
- Proposed label (Submission 0001); and
- Study YKP3089C020 clinical trial report, cardiac safety report, and C-QT report (Submission 0001).

1 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 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time	ΔΔQTcF (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.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 ADDITIONAL COMMENTS TO THE REVIEW DIVISION

- There was 1 death in this study. Subject (b) (6) was discontinued from the study due to the SAE of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome that began on Day 32 of dosing (200 mg cenobamate QD). Subject (b) (6) subsequently died from the SAE of eosinophilic myocarditis (verbatim term: cardiac dysrhythmia due to eosinophilic myocarditis due to DRESS) on Day 87.
- The available nonclinical information suggests that the observed QTc shortening is mediated via blockade of the cardiac sodium channel (Appendix 5). Some drugs that inhibit the cardiac sodium channel have been observed to increase mortality in patients with structural heart disease in the CAST trials (i.e., encainide, flecainide and moricizine) and IMPACT study (i.e., mexiletine). Whether or not cenobamate carries the same risk is unknown. Additionally, some sodium channel blocking drugs (i.e., lacosamide and lamotrigine) have been observed to have a potential for unmasking Brugada syndrome. Due to cenobamate's inhibition of the cardiac sodium channel it is possible that cenobamate carries a similar risk.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Because the nonclinical information suggests that the QTc shortening is due to sodium channel blockade, we recommend additional nonclinical experiments to determine the anti-arrhythmic class of cenobamate, as that information would be useful to better understand the potential risk for cenobamate.

2.2 PROPOSED LABEL

We recommend including a warning for QT shortening, similar to the warning in the label for BANZEL [see *QT Shortening* (section 5.3)].

Below are proposed edits to section 12.2 of the label submitted to SDN 0001 (link) . Our changes are highlighted (addition, ~~deletion~~). These are suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology (b) (4) In a placebo-controlled QT study in healthy volunteers, dose-dependent shortening of the QTcF interval has been observed with TRADENAME. The mean ΔΔQTc is -11 [-13, -8] ms for 200 mg QD and -18 [-22, -15] ms for 500 mg QD. 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.
Because of the magnitude of QTc shortening observed in the thorough QT study, we propose to report the shortening by dose in the label.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the QT assessment proposal previously (DARRTS 02/19/2015), which described a concern about whether or not the timing of ECG/PK collection would cover major metabolites. The sponsor clarified that the metabolites in the CP table were not major and as a result the QT-IRT agreed to the timing of ECG/PK collection (DARRTS 04/27/2015).

This QT assessment is based on a thorough QT study using a nested crossover study design and the primary endpoint is based on by-time analysis. At the time of last review, the therapeutic dose is anticipated to be 100 to 200 mg QD. (b) (4)

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

Cenobamate excluded the 10 ms threshold at the supratherapeutic dose level. But QT shortening effect was observed. The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. Both FDA's analysis and sponsor's analysis confirm that the assay sensitivity was established. Please see section 4.3 for additional details.

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

Sponsor provided categorical analysis of QTcF for >450 ms, >480 ms and >500 ms categories. FDA analysis shows shortening effect. So in addition to sponsor's analysis, FDA reviewer also performed categorical analysis for minimum values of QTcF and ΔQTcF. FDA reviewer performed standard categorical analysis for other intervals such as PR, HR and QRS. Sponsor provided categorical analysis for different intervals. For example, FDA reviewer provide number of subjects who experienced QRS interval greater than 110 ms and sponsor provided QRS interval greater than 120 ms. So, the tables are not directly comparable. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

There was 1 death in this study. Subject (b) (6) (a 38-year-old White Hispanic female) was discontinued from the study due to the SAE of DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome that began on Day 32 of dosing (200 mg cenobamate QD). Subject (b) (4) subsequently died from the SAE of eosinophilic myocarditis (verbatim term: cardiac dysrhythmia due to eosinophilic myocarditis due to DRESS) on Day 87.

There were no other SAEs in this study.

Three subjects discontinued due to AEs when taking cenobamate: Subject (b) (4) was discontinued by the PI due to the AE of lip swelling on Day 31; Subject (b) (4) withdrew consent from the study due to the AE of vomiting on Day (b) (4), and Subject (b) (4) was discontinued by the PI due to the AE of macular rash on Day (b) (4)

Reviewer's comment: *Besides Subject (b) (6) who died from eosinophilic myocarditis due DRESS, no other significant cardiac adverse events were detected.*

3.2.4 Exposure-Response Analysis

The relationship between ΔΔQTcF and cenobamate plasma concentrations was investigated by a linear mixed-effects modeling approach. Time-matched concentration was included in the model as a covariate and subject as a random effect for both intercept and slope, whenever applicable. The sponsor's analysis predicted a concentration-dependent decrease in ΔΔQTcF. The predicted ΔΔQTcF at geometric mean peak concentrations were -9.9 ms (90% CI: -11.6 ms, -8.1 ms) and -17.1 ms (90% CI: -19.5 ms, -14.8 ms) on day 35 (200 mg QD) and on day 63 (500 mg QD), respectively.

The reviewer's analysis also shows a concentration-dependent decrease, but the relationship is not linear. Please see section 4.5 for additional details.

4 REVIEWERS' ASSESSMENT

4.1 Evaluation of the QT/RR Correction Method

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e., mean < 10 bpm) were observed (see Sections 4.3.2 and 4.5).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not conducted.

4.3 CENTRAL TENDENCY ANALYSIS

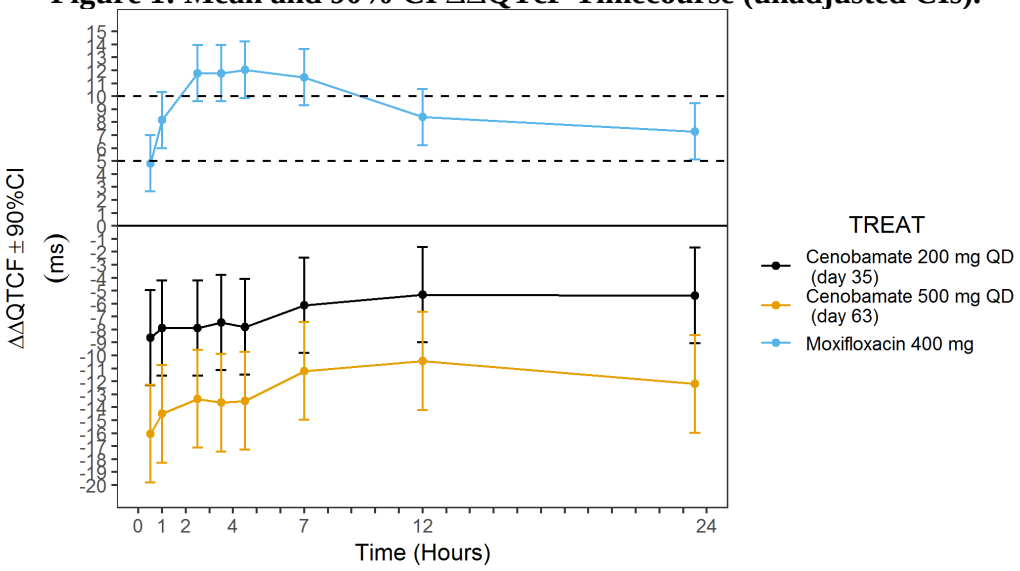
4.3.1 QTc

The statistical reviewer used a linear mixed model to analyze the ΔQTcF effect of the cenobamate and used a subset of the data (parallel design part). The model included treatment (cenobamate and matched placebo arms), time, time by treatment interaction as fixed effects. The analysis was conducted by day, i.e. separately for day 35 and day 63. Subjects were included in the model as a random effect. Baseline values were also included in the model as a covariate. The results are presented in Table 2. Overall, the reduction in change from baseline in QTcF was observed. The smallest lower bound of the 90% confidence interval on ΔΔQTcF is -19.8 ms for cenobamate 500 mg QD on day 63.

Table 2: Analysis Results of ΔQTcF and ΔΔQTcF for Cenobamate

	Treatment Group							
	Cenobamate 200 mg QD (day 35)				Cenobamate 500 mg QD (day 63)			
	ΔQTcF	Placebo	ΔΔQTcF		ΔQTcF	Placebo	ΔΔQTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-9.9	-1.3	-8.6	(-12.3, -5)	-20.2	-4.1	-16.0	(-19.8, -12.3)
1	-7.7	0.2	-7.9	(-11.6, -4.2)	-17.2	-2.7	-14.5	(-18.3, -10.7)
2.5	-6.1	1.8	-7.9	(-11.6, -4.2)	-15.0	-1.7	-13.3	(-17.1, -9.6)
3.5	-6.6	0.8	-7.5	(-11.1, -3.8)	-15.4	-1.7	-13.6	(-17.4, -9.9)
4.5	-6.0	1.8	-7.8	(-11.5, -4.1)	-15.1	-1.6	-13.5	(-17.3, -9.7)
7	-7.4	-1.2	-6.1	(-9.8, -2.5)	-16.0	-4.8	-11.2	(-15, -7.4)
12	-4.8	0.5	-5.3	(-9, -1.6)	-13.1	-2.6	-10.4	(-14.2, -6.6)
23.5	-6.1	-0.7	-5.4	(-9.1, -1.7)	-14.0	-1.8	-12.2	(-16, -8.4)

Figure 1: Mean and 90% CI ΔΔQTcF Timecourse (unadjusted CIs).



4.3.1.1 Assay sensitivity

The statistical reviewer used the subset of data (crossover design part) for assay sensitivity analysis. The linear mixed model to analyze the ΔQTcF effect included treatment (moxifloxacin and matched placebo), time, time by treatment interaction and sequence as fixed effects. Subjects were included in the model as a random effect. Baseline values were also included in the model as a covariate. The results are presented in Table 3. In QTcF correction method, the largest lower bound of the unadjusted 90% confidence interval is 9.9 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 9.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study. The time profile of moxifloxacin is consistent with ascending, peak, and descending phase of historical moxifloxacin profile. Overall, assay sensitivity was demonstrated in this study.

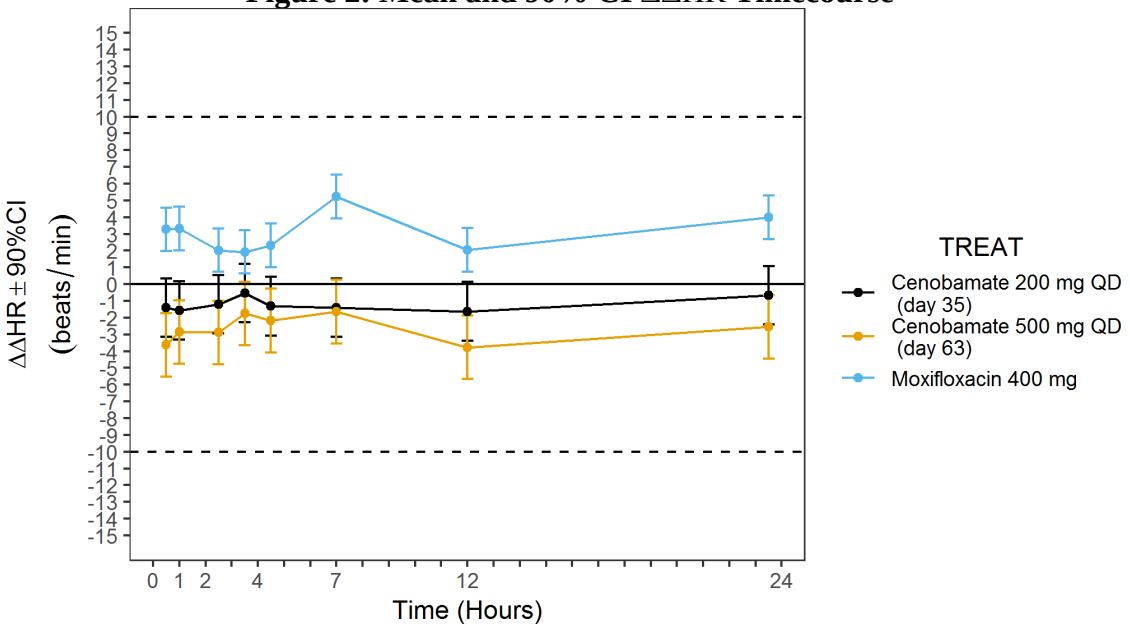
Table 3: Analysis Results of ΔQTcF and ΔΔQTcF for moxifloxacin

Treatment Group (Moxifloxacin 400 mg)					
	ΔQTcF	Placebo	ΔΔQTcF		
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
0.5	6.4	1.6	4.8	(2.7, 7.0)	(1.9, 7.8)
1	12.5	4.3	8.2	(6.0, 10.3)	(5.2, 11.1)
2.5	13.5	1.7	11.8	(9.6, 13.9)	(8.8, 14.7)
3.5	15.0	3.2	11.8	(9.6, 14.0)	(8.8, 14.7)
4.5	15.5	3.4	12.0	(9.9, 14.2)	(9.1, 15.0)
7	2.1	-9.4	11.5	(9.3, 13.6)	(8.5, 14.4)
12	7.7	-0.7	8.4	(6.2, 10.6)	(5.4, 11.4)
23.5	7.7	0.4	7.3	(5.1, 9.5)	(4.3, 10.3)

4.3.2 HR

The same statistical analysis as in the primary analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between cenobamate 200 mg QD (day 35) and placebo and cenobamate 500 mg QD (day 63) and placebo are 1.2 bpm and -1.9 bpm, respectively.

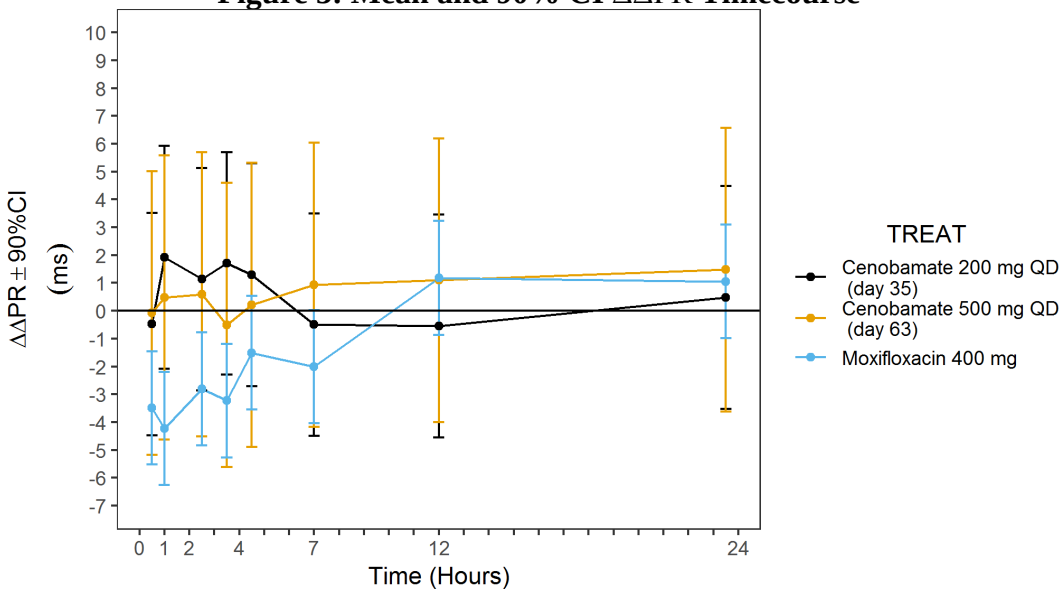
Figure 2: Mean and 90% CI ΔΔHR Timecourse



4.3.3 PR

The same statistical analysis as in the primary analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between differences between cenobamate 200 mg QD (day 35) and placebo and cenobamate 500 mg QD (day 63) and placebo are 5.9 ms and 6.6 ms, respectively.

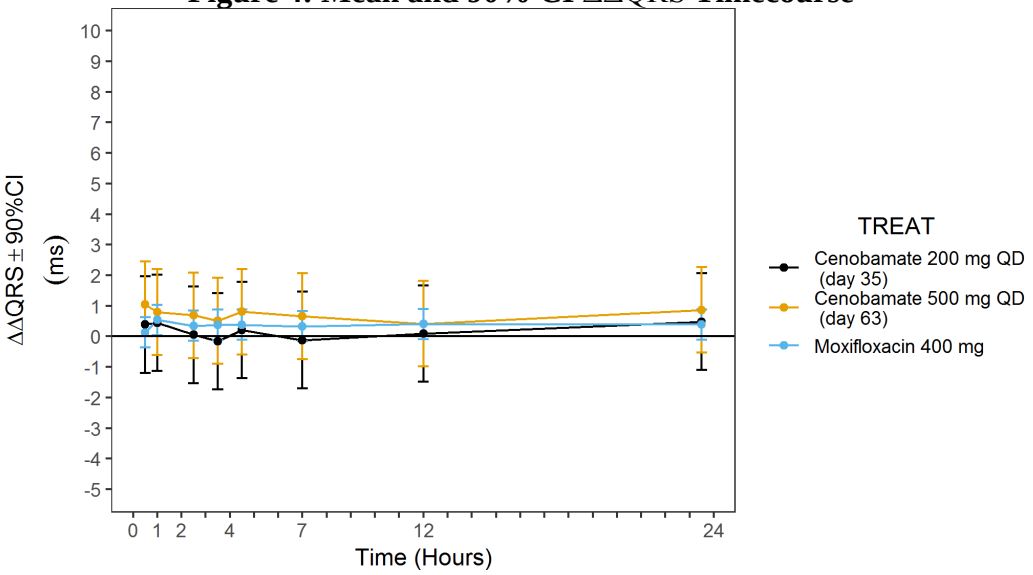
Figure 3: Mean and 90% CI ΔΔPR Timecourse



4.3.4 QRS

The same statistical analysis as in the primary analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between differences between cenobamate 200 mg QD (day 35) and placebo and cenobamate 500 mg QD (day 63) and placebo are 2.1 ms and 2.4 ms, respectively.

Figure 4: Mean and 90% CI ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis of QTcF, PR, QRS and HR included data from parallel part of the study design. All post-baseline ECG data were collected at scheduled visits.

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 4: Categorical Analysis for maximum QTcF

Treatment	Day	Total (N)		Value <= 450 ms		450 ms < Value <= 480 ms	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	50 (98.0%)	403 (99.5%)	1 (2.0%)	2 (0.5%)
Cenobamate 500 mg QD	63	50	398	50 (100.0%)	398 (100.0%)	0	0
Placebo	35	54	428	51 (94.4%)	411 (96.0%)	3 (5.6%)	17 (4.0%)
Placebo	63	52	410	50 (96.2%)	400 (97.6%)	2 (3.8%)	10 (2.4%)

Note: Subjects were counted in their maximum categories.

Table 5 lists the number of subjects as well as the number of observations whose QTcF values are between 320 ms and 350 ms, between 350 ms and less or equal to 400 ms and

greater than 400 ms. Two and four subjects had QTcF between 320 ms and 350 ms for cenobamate 200 mg QD (day 35) and 500 mg QD (day 63) respectively.

Table 5: Categorical Analysis for minimum QTcF

Treatment	Day	Total (N)		320 ms < Value <= 350 ms		350 ms < Value <= 400 ms		Value >= 400 ms	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	2 (3.9%)	4 (1.0%)	38 (74.5%)	235 (58.0%)	11 (21.6%)	166 (41.0%)
Cenobamate 500 mg QD	63	50	398	4 (8.0%)	5 (1.3%)	38 (76.0%)	289 (72.6%)	8 (16.0%)	104 (26.1%)
Placebo	35	54	428	1 (1.9%)	1 (0.2%)	34 (63.0%)	222 (51.9%)	19 (35.2%)	205 (47.9%)
Placebo	63	52	410	0	0	38 (73.1%)	226 (55.1%)	14 (26.9%)	184 (44.9%)

Note: Subjects were counted in their minimum categories.

Table 6 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 30 ms in the cenobamate group for both dose levels.

Table 6: Categorical Analysis of maximum ΔQTcF

Treatment	Day	Total (N)		Value <= 30 ms	
		# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	51 (100.0 %)	405 (100.0 %)
Cenobamate 500 mg QD	63	50	398	50 (100.0 %)	398 (100.0 %)
Placebo	35	54	428	54 (100.0 %)	428 (100.0 %)
Placebo	63	52	410	52 (100.0 %)	410 (100.0 %)

Note: Subjects were counted in their maximum categories.

Table 7 lists the categorical analysis results for ΔQTcF. There are 3 subjects who experienced ΔQTcF ≤ -40 ms for cenobamate 500 mg (day 63).

Table 7: Categorical Analysis of minimum ΔQTcF

Treatment	Day	Total (N)		Value <= -40 ms		-40 ms > Value <= -20 ms		-20 ms > Value	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	0	0	16 (31.4%)	47 (11.6%)	35 (68.6%)	358 (88.4%)
Cenobamate 500 mg QD	63	50	398	3 (6.0%)	6 (1.5%)	33 (66.0%)	162 (40.7%)	14 (28.0%)	230 (57.8%)
Placebo	35	54	428	0	0	3 (5.6%)	3 (0.7%)	51 (94.4%)	425 (99.3%)

Treatment	Day	Total (N)		Value <= -40 ms		-40 ms > Value <= -20 ms		-20 ms > Value	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	63	52	410	0	0	9 (17.3%)	16 (3.9%)	43 (82.7%)	394 (96.1%)

Note: Subjects were counted in their minimum categories.

4.4.2 PR

The outlier analysis results for PR are presented in Table 8. There is one subject who experienced PR interval greater than 200 ms for both doses of cenobamate.

Table 8: Categorical Analysis for PR

Treatment	Day	Total (N)		Value <= 200 ms		200 ms < Value <= 220 ms	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	50 (98.0%)	404 (99.8%)	1 (2.0%)	1 (0.2%)
Cenobamate 500 mg QD	63	50	398	49 (98.0%)	396 (99.5%)	1 (2.0%)	2 (0.5%)
Placebo	35	54	428	53 (98.1%)	426 (99.5%)	1 (1.9%)	2 (0.5%)
Placebo	63	52	410	51 (98.1%)	409 (99.8%)	1 (1.9%)	1 (0.2%)

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 9. There are 8 subjects and 7 subjects who experienced QRS interval greater than 110 ms for cenobamate 200 mg QD (day 35) and 500 mg QD (day 63) respectively.

Table 9: Categorical Analysis for QRS

Treatment	Day	Total (N)		Value <= 100 ms		100 < Value <= 110 ms		Value > 110 ms	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Cenobamate 200 mg QD	35	51	405	18 (35.3%)	175 (43.2%)	25 (49.0%)	190 (46.9%)	8 (15.7%)	40 (9.9%)
Cenobamate 500 mg QD	63	50	398	16 (32.0%)	155 (38.9%)	27 (54.0%)	209 (52.5%)	7 (14.0%)	34 (8.5%)
Placebo	35	54	428	20 (37.0%)	186 (43.5%)	27 (50.0%)	208 (48.6%)	7 (13.0%)	34 (7.9%)
Placebo	63	52	410	21 (40.4%)	192 (46.8%)	27 (51.9%)	206 (50.2%)	4 (7.7%)	12 (2.9%)

4.4.4 HR

There are no subjects who experienced HR greater than 100 bpm in the cenobamate group for both doses.

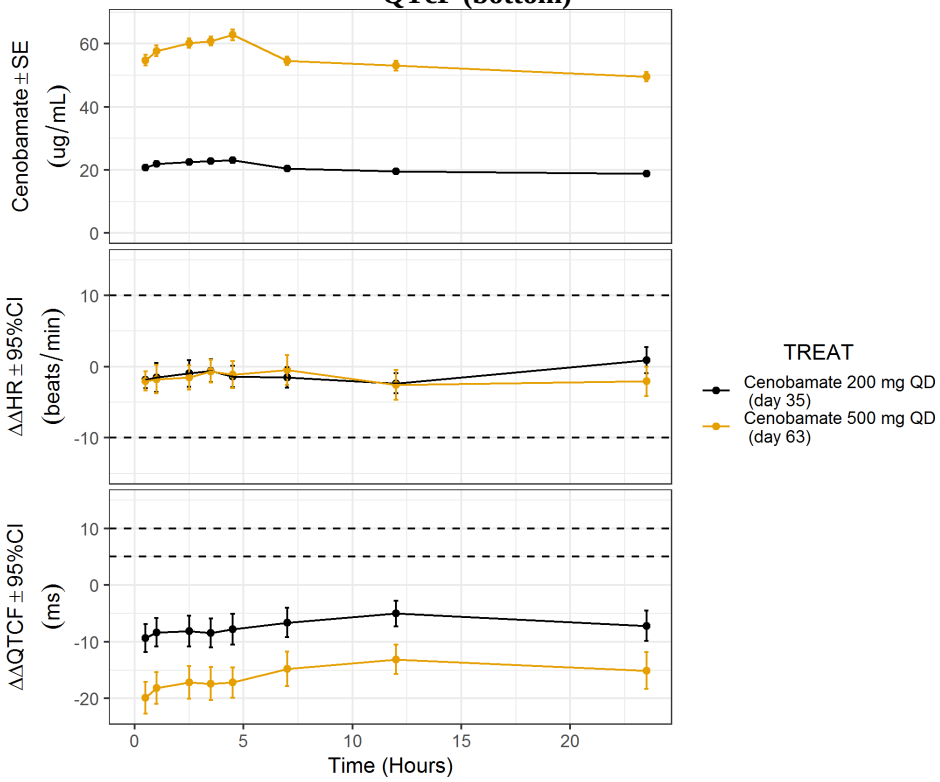
4.5 EXPOSURE-RESPONSE ANALYSIS

4.5.1 QTc

The objective of the clinical pharmacology analysis is to assess the relationship between cenobamate concentration and ΔQTcF.

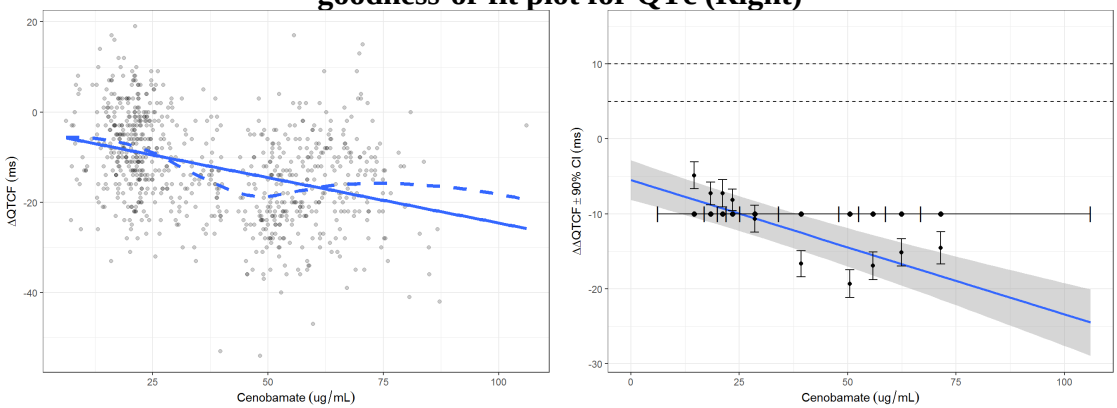
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTcF and 3) presence of non-linear relationship. An evaluation of the time-course of drug concentration and changes in ΔΔHR and ΔΔQTcF is shown in Figure 5. Day 35 corresponds to the steady state of 200 mg QD, and day 63 corresponds to the steady state of 500 mg QD. The figure shows an absence of significant changes in HR. There is dose-dependent increase in cenobamate exposure, and a clear separation in the ΔΔQTcF profiles on the two dose levels. Within each dosing period, there appears to be a slight increase in ΔΔQTcF that did not correspond to the T_{max} of cenobamate. The figure does not appear to show significant hysteresis. The very small fluctuation in cenobamate exposure at steady state makes it difficult to identify potential hysteresis.

Figure 5: Time course of drug concentration (top), heart rate (middle) and QTcF (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between drug concentration and ΔQTcF and the goodness-of-fit plot of a linear model. The figure shows a decrease in ΔQTcF with concentration that is not linear.

Figure 6: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right)



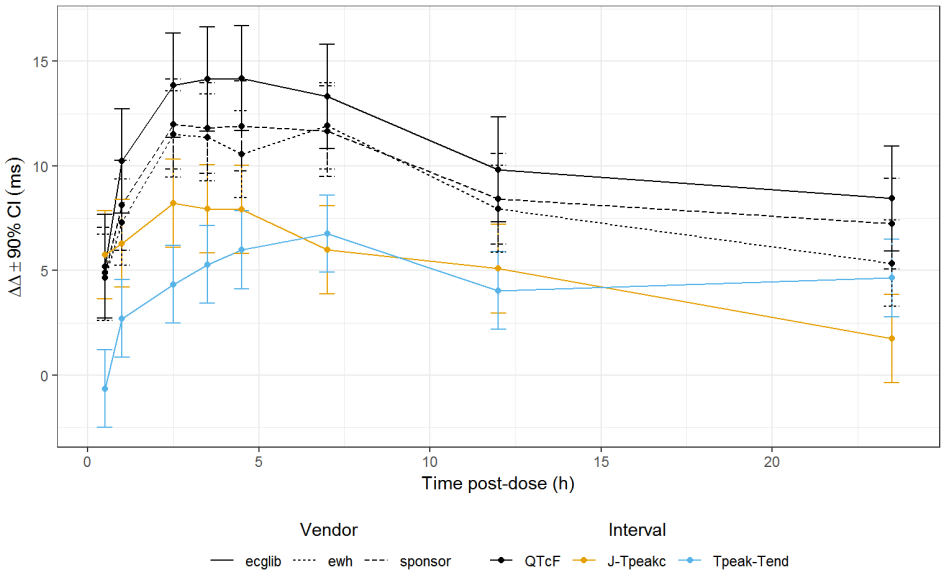
4.5.1.1 Assay sensitivity

Assay sensitivity was established using central tendency analysis. Please see section 4.3.1.1 for additional details.

4.5.2 Other ECG Intervals

The nonclinical data for cenobamate suggests that cenobamate blocks the cardiac sodium channel and the hERG potassium channel (Appendix 5) and the concentration-response relationship was therefore explored for other ECG biomarkers: J-Tpeakc and Tpeak-Tend. The changes in other ECG biomarkers for moxifloxacin are shown in Figure 7 showing the expected time-course, i.e., increase in J-Tpeakc and Tpeak-Tend.

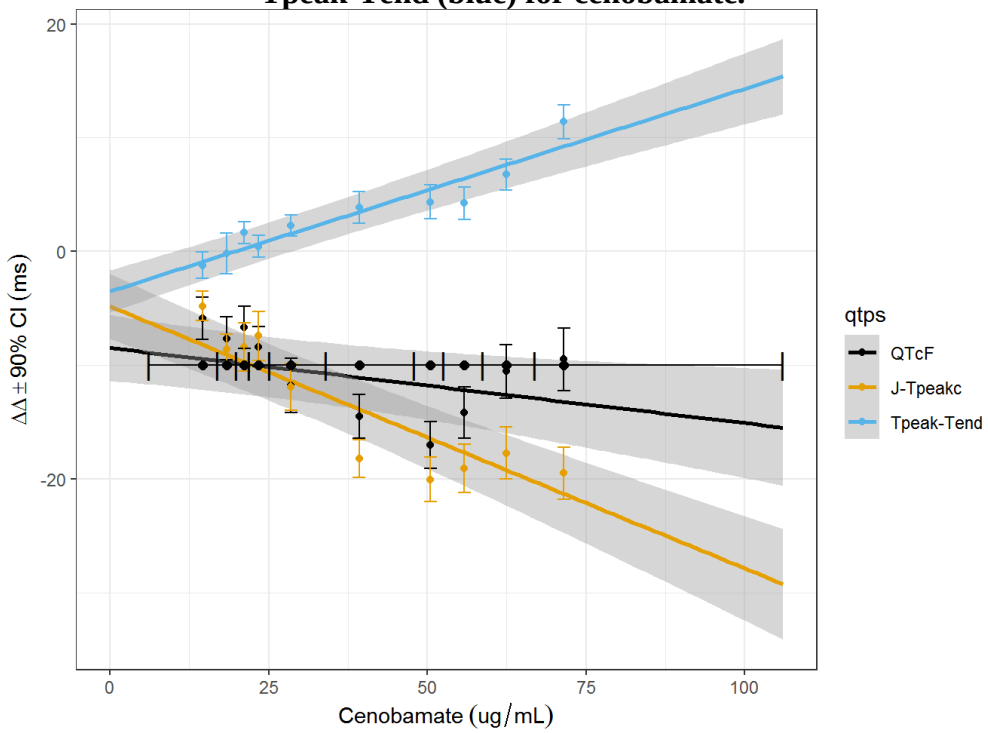
Figure 7: Time-course for QTcF (black); J-Tpeakc (orange) and Tpeak-Tend (blue) for moxifloxacin.



A similar analysis was conducted for cenobamate, which shows an increase in Tpeak-Tend and a decrease in J-Tpeakc (Figure 8). The increase in Tpeak-Tend and shortening of J-Tpeakc is suggestive of the presence of inhibition of multiple cardiac ionic currents,

likely hERG and sodium, consistent with the nonclinical results. However, the interpretation of the apparent U-shape in the QTcF interval when using a different ECG algorithm is less clear.

Figure 8: concentration-response analysis for QTcF (black); J-Tpeakc (orange) and Tpeak-Tend (blue) for cenobamate.



4.6 SAFETY ASSESSMENTS

This section describes safety assessment for the clinical studies. See section 3.2.3 for safety assessments in the thorough QT study.

4.7 PR AND QRS

No clinically relevant changes in PR and QRS were observed in this study.

5 REVIEW OF SUPPORTING NONCLINICAL INFORMATION

5.1 PATCH CLAMP EXPERIMENTS

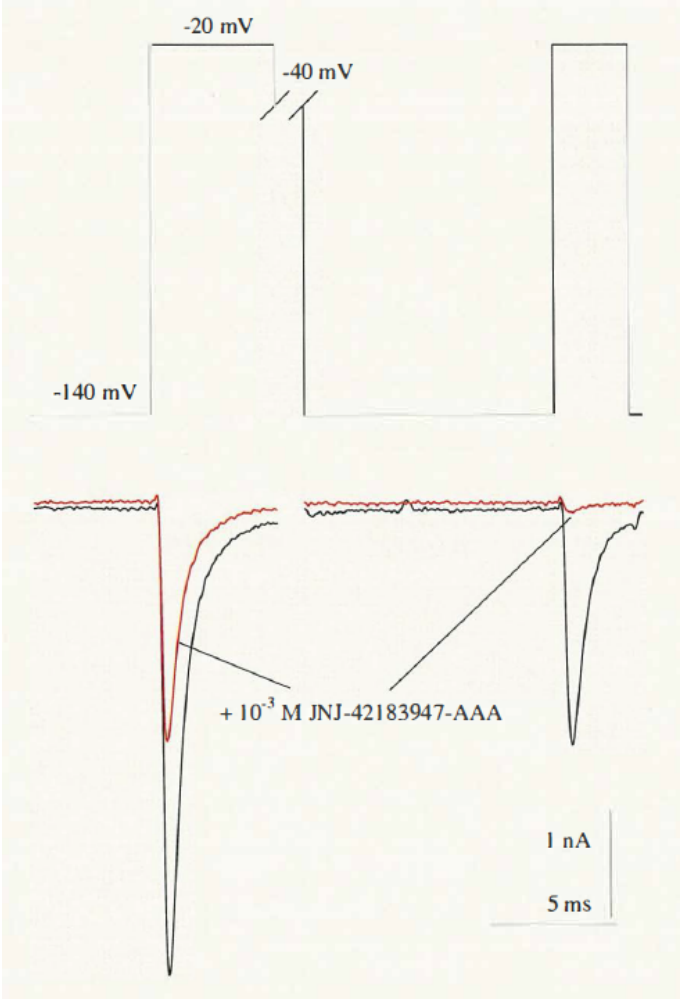
The sponsor has evaluated the effects of cenobamate on hERG, L-type calcium and sodium (NaV 1.5).

An early non-GLP study evaluating the effects of hERG suggested an IC50 of 16.9 uM (8427). The sponsor notes that due to lack of standardization of experimental conditions that the hERG assessment was repeated first using CHO cells (SK08TR1) and subsequently using HEK-293 (SK16011), with the latter being a GLP study. The IC50s obtained in SK08TR1 and SK16011 are similar (1869 uM vs 1600 uM) and suggests that cenobamate has the potential to directly inhibit hERG (safety margin: 23 to 27) using the free Cmax for the highest proposed therapeutic dose (400 mg) of 67 uM.

The sponsor also evaluated the potential for direct inhibition of the L-type calcium current in (151124tli). This study only included two dose levels (30 and 100 uM) and showed a dose-dependent increase (30 uM: 2.7%; 100 uM: 7%) in the mean current inhibited, however, due to the low doses relative to free Cmax (67 uM) included it is not possible to comment on the potential for direct inhibition of the L-type calcium current by cenobamate.

The effects of cenobamate on NaV 1.5 was also evaluated in two studies PHARM-NJ-SM-20 and SK08025. PHARM-NJ-SM-20 was conducted in CHO cells using a voltage protocol consisting of an initial step to -20 mV from -140 mV followed by sodium channel inactivation by stepping to -40 mV for 10 s, then a 10 ms step to -140 mV and a 3 ms step to -20 mV. The voltage protocol and current traces from a cell in either control conditions (black) or 1000 uM of cenobamate are shown in Figure 9. The peak sodium current was measured during the -20 mV steps and reduction in these two peak currents reflect peak sodium current reduction and inhibition of inactivated sodium channels.

Figure 9: Pulse protocol used (top) and superimposed current traces (bottom) for control condition (black) and 1000 uM cenobamate (red)

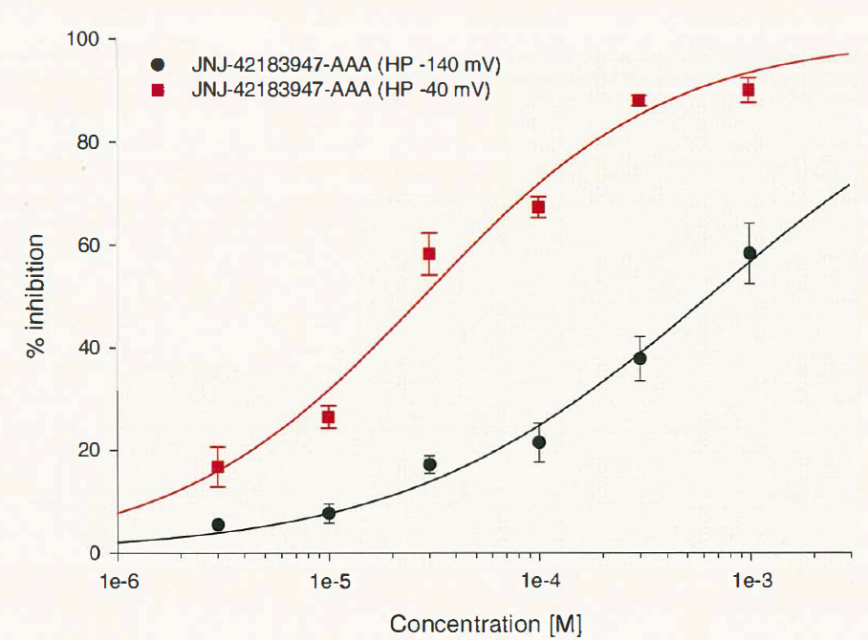


Source: PHARM-NJ-SM-20, Figure 1

The experiments were carried out with multiple dose levels of cenobamate (3, 10, 30, 100, 300, 1000 uM) as well as lidocaine (10, 100, 1000 uM). At each dose level for cenobamate

and lidocaine the reduction in peak sodium current was calculated for each of the two -20 mV pulses and the results for cenobamate is shown in Figure 10 and Table 10 summarizes the results for both cenobamate and lidocaine.

Figure 10: dose-response curves for cenobamate for peak current reduction for the first peak following a -140 mV (black) holding potential (HP) and at the second peak following a HP of -40 mV (red)



Source: PHARM-NJ-SM-20, Figure 3

The results suggest that cenobamate reduces the peak current measured following both holding potentials (-140 mV and -40 mV), but with a greater reduction for the second peak current. These results are consistent with those of the positive control, lidocaine, and suggests that cenobamate preferentially inhibits sodium channels in the inactivated state.

The sponsor conducted another study of the effects of cenobamate on the peak sodium current as well as voltage-dependent activation, inactivation, recovery from inactivation and use and frequency dependence (SK08025). This study showed minimal decrease of the peak current at 100 uM (10 to 13%). However, using a pulse protocol with varying pre-pulse duration showed that at longer pre-pulse durations (> 0.02 s) that there was an increase in the reduction of the sodium current by 30 uM of cenobamate suggesting that cenobamate blocks sodium currents in the inactivated state.

Table 10: Inhibition of sodium current at different holding potentials (see Figure 9 for additional details on the protocol)

		Mean inhibition (%) ± SEM			
		HP –140 mV		HP –40 mV	
	Conc. (M)	Test drug	Solvent control	Test drug	Solvent control
JNJ-42183947-AAA	3×10^{-6}	5.5 ± 0.6 (n = 6)	3.1 ± 0.9 (n = 7)	16.8 ± 3.9 (n = 6)#	2.9 ± 1.4 (n = 7)
	1×10^{-5}	7.7 ± 1.9 (n = 6)	3.1 ± 0.9 (n = 7)	26.5 ± 2.2 (n = 6)#	2.9 ± 1.4 (n = 7)
	3×10^{-5}	17.2 ± 1.7 (n = 6)#	6.9 ± 1.7 (n = 7)	58.2 ± 4.1 (n = 6)#	7.0 ± 2.5 (n = 7)
	1×10^{-4}	21.5 ± 3.8 (n = 6)#	6.9 ± 1.7 (n = 7)	67.3 ± 2.0 (n = 6)#	7.0 ± 2.5 (n = 7)
	3×10^{-4}*	37.8 ± 4.3 (n = 6)#	9.6 ± 3.0 (n = 7)	88.0 ± 1.0 (n = 6)#	11.6 ± 2.7 (n = 7)
	1×10^{-3}*	58.3 ± 5.9 (n = 6)#	9.6 ± 3.0 (n = 7)	90.0 ± 2.4 (n = 6)#	11.6 ± 2.7 (n = 7)
Lidocaine	1×10^{-5}	1.8 ± 1.5 (n = 5)	3.1 ± 0.9 (n = 7)	29.0 ± 2.6 (n = 5)#	2.9 ± 1.4 (n = 7)
	1×10^{-4}	20.0 ± 4.5 (n = 5)#	6.9 ± 1.7 (n = 7)	79.6 ± 1.7 (n = 5)#	7.0 ± 2.5 (n = 7)
	1×10^{-3}	59.2 ± 4.8 (n = 5)#	9.0 ± 3.1 (n = 7)	90.8 ± 2.3 (n = 5)#	10.9 ± 2.9 (n = 7)

n = number of cells tested
# $p \leq 0.05$
* NB: Analysis revealed low recovery of the locally-applied drug concentration (i.e. 65% at 3×10^{-4} M and 82% at 10^{-3} M).

Source: PHARM-NJ-SM-20, Table 1

5.2 ISOLATED RABBIT PURKINJE FIBER

The impact on action potential duration and morphology was evaluated using isolated rabbit Purkinje fibers (PHARM-NJ-SM-21) at multiple doses of cenobamate (1, 10 and 100 uM) at a stimulation frequency of 1 Hz for 60 min followed by 0.2 and 2 Hz for 5 min each. Example traces are shown in Figure 11.

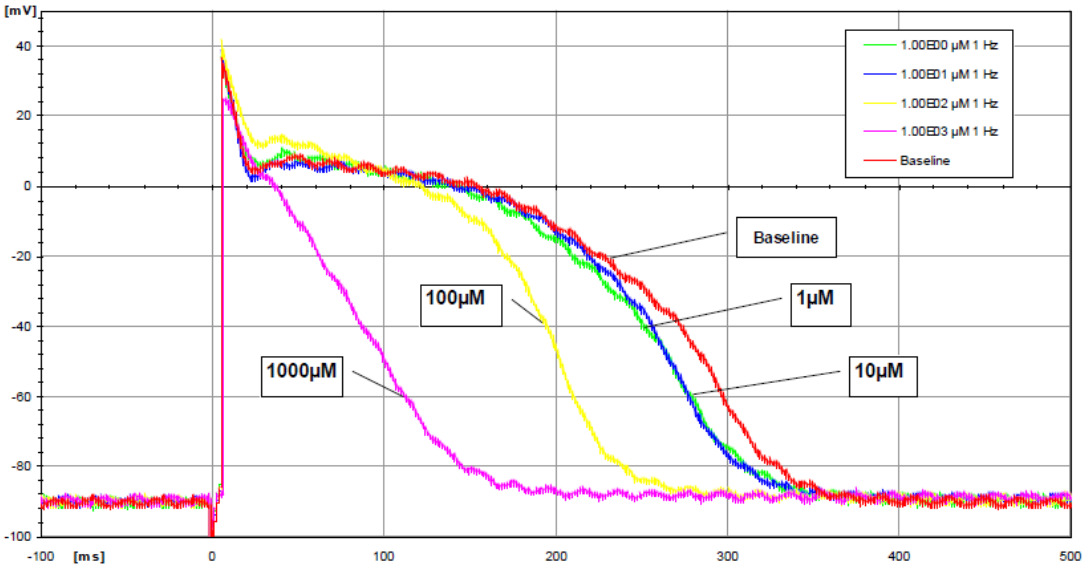
The results of the isolated rabbit Purkinje fiber experiments are shown in Table 11 and shows a dose-dependent decreases in APD50 and APD90 and a decrease in APA and Vmax at 1000 uM.

Table 11: Changes in Purkinje fiber action duration and morphology for vehicle control and cenobamate at different stimulation frequencies

Parameter	Treatment	Baseline	Changes	1µM	10µM	100µM	1000µM	1000µM	1000µM
			as	15 min	15 min	15 min	15 min	5 min	5 min
		1 Hz		1 Hz	1 Hz	1 Hz	1 Hz	0.2 Hz	2 Hz
AAP	Compound	139	Δ%	1	1	-2	***-19***	-25	***-31***
mV	Vehicle	138		0	-1	-1	-3	-9	1
APD_{40} LV en	Compound	110	Δ%	-	-	-	-	-	-
ms	Vehicle	181		-6	-2	-6	1	62	-29
APD_{50} LV en	Compound	184	Δ%	-14	-18	***-53***	***-78***	***-84***	***-76***
ms	Vehicle	227		-6	-1	-3	-1	60	-20
APD_{90} LV en	Compound	264	Δ%	-4	-5	***-30***	***-48***	***-43***	***-51***
ms	Vehicle	283		-3	-1	0	1	59	-18
Triang 90-40	Compound	141	Δ%	-	-	-	-	-	-
ms	Vehicle	100		2	3	11	7	48	-2
Vmax	Compound	667	Δ%	-5	-4	-8	***-54***	-72	***-75***
V/s	Vehicle	760		-3	-10	-11	-11	-37	-3
RMP	Compound	-90	Δ%	-2	0	-4	***-9***	-7	***-16***
mV	Vehicle	-90		-1	-1	0	-1	-7	0

Source: PHARM-NJ-SM-21, Table 3

Figure 11: Example of changes in AP for different doses of cenobamate at 1 Hz



Source: PHARM-NJ-SM-21, Figure 2

5.3 SUMMARY

Overall, the results of the patch clamp experiments for cenobamate suggest that blockade of cardiac sodium channels, blockade of hERG potassium channels and the impact on the L-type calcium current is inconclusive. While, further evaluation of sodium channel

kinetics suggests that cenobamate appear to exhibit state-dependent block of the sodium channel similar to lidocaine, it is not possible to determine the antiarrhythmic class of cenobamate. These results are consistent with the observed APD shortening observed in the isolated rabbit Purkinje fiber experiments and reduction in Vmax at higher concentrations.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 18, 2019
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212839
Product Name and Strength:	Xcopri (cenobamate) tablets, 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	SK Life Science, Inc.
FDA Received Date:	November 21, 2018
OSE RCM #:	2018-2559
DMEPA Safety Evaluator:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review is in response to a request from the Division of Neurology Products (DNP) to review the proposed labels and labeling for Xcopri (cenobamate) tablets for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI) identified the following areas of needed improvement:

- We note the important administration warning "Do not crush or chew" does not appear in Section 2.1 *Important Administration Instructions* of the proposed PI which poses risk of wrong technique medication errors.
- We note what appears to be an error in Section 17 *Patient Counseling Information* of the PI: the reader is directed to reference an incorrect section of the PI, which may lead to confusion.

We note nineteen different packaging configurations are proposed. We find both the quantity and current presentation of the packaging configurations to be overly complex and prone to selection errors at the prescribing and dispensing phases of the medication use system.

Due to our aforementioned concerns with the packaging configurations, we find it premature to evaluate the Section 16 'How Supplied/Store and Handling' of the PI. Our assessment, and corresponding recommendations, will be provided under a separate cover once the Sponsor

addresses our concerns with the packaging configurations (see Recommendation A.1 in Section 4.2 below).

Our review of the proposed container labels identified areas which may be improved to decrease risk of medication error. We note the following:

- The format for the expiration date is not defined, which poses risk of deteriorated drug medication errors.
- The format of the temperature statement on the container labels and carton labeling is inconsistent with the format of the temperature statement in Section 16.2 *Storage and Handling* of the Prescribing Information, which could pose risk of confusion and drug degradation medication errors.
- The net quantity statement appears in close proximity to the product strength on the bottle container labels. From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
- The (b) (4) may lead to wrong strength selection errors.
- The presence of the (b) (4) statement (b) (4) on the Principal Display Panel (PDP) of the bottle container labels is duplicative, and causes the PDP to appear visually cluttered which may hinder the readability of other important information.
- The strength expression on the Principal Display Panel (PDP) on all the maintenance and titration packs is not congruent with how the product is expected to be prescribed and is prone to confusion and wrong strength medication errors.
- The strength expression of the daily dose inside the blister wallet labeling on some of the maintenance and titration packs is not clear and may lead to wrong dose medication errors. (See Figure 1 below)

(b) (4)

Figure 1

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to ensure safe and effective use and handling of the proposed product. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Sponsor. We recommend these recommendations are implemented prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. The important administration warning "Do not crush or chew" appears in Section 17 *Patient Counseling Information* of the PI and the proposed Medication Guide. However, this important administration warning does not appear in Section 2.1 *Important Administration Instructions* of the proposed PI which poses risk of wrong technique medication errors. We recommend revising the warning "Swallow whole" to read "Swallow whole. Do not crush or chew" in Section 2.1 of the PI to minimize the risk of wrong technique administration errors.
2. The following dosing instructions in Section 17 *Patient Counseling Information* of the PI: "Counsel patients that TRADENAME may be taken at any time with or without food. Instruct patients that TRADENAME tablets should be swallowed whole with liquid and not chewed or crushed" refers the reader to "see Dosage and Administration (b) (4)". However, the aforementioned information is contained within Section 2.1 of the PI (b) (4) We recommend revising the statement in Section 17 *Patient Counseling Information* of the PI to read "see Dosage and Administration (2.1)" to minimize the risk of confusion.

4.2 RECOMMENDATIONS FOR SK LIFE SCIENCE, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Packaging Configurations)

1. You propose nineteen different packaging configurations. We find both the quantity of packaging configurations (i.e., 19 variations) and current presentation of the packaging configurations (e.g. (b) (4) in the titration pack) to be overly complex and prone to selection errors at the prescribing and dispensing phases of the medication use system. Although we agree that special titration blister packaging for specific treatment regimens might improve patient convenience and minimize the risk of accidental exposure to the drug, we find the quantity and current presentation of your proposed packaging configurations may lead to confusion, medication errors, and an increased pill burden. We recommend you limit the number and variety of packaging configurations (i.e. bulk bottle, titration packs, maintenance packs) to those necessary to support the dosage and administration of the drug product in the intended patient population.

B. General Comments (Container labels & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD

format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

2. As currently presented, the temperature statement on the container labels and carton labeling (68-77°F [20-25°C]) is not expressed in the same format as the temperature statement in Section 16.2 *Storage and Handling* of the Prescribing Information (20-25°C [68-77°F]), which could pose risk of confusion and drug degradation medication errors. Revise the temperature statement on the container labels and carton labeling to read:

   Tablets should be stored at controlled room temperature 20°C to 25°C (68°F to 77°F) with excursions allowed between 15°C to 30°C (59°F to 86°F).

3. We recommend adding the important administration warning "Swallow whole - Do not crush or chew" to the Principal Display Panel (PDP) to minimize the risk of wrong technique administration errors.

C. Container Labels (Bottles)

1. The net quantity statement appears in close proximity to the product strength on the bottle container labels. From postmarketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel.

2. The (b) (4) may lead to wrong strength selection errors. (See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors; April 2013*). Consider utilizing (b) (4)

3. The presence of the (b) (4) statement (b) (4) on the Principal Display Panel (PDP) of the bottle container labels is duplicative, causes the PDP to appear visually cluttered and my hinder the readability of other important information. To minimize visual clutter and improve readability, remove the statement (b) (4) from the PDP of the bottle container labels.

D. Container Labels (Maintenance & Titration Packs)

1. The strength expression on the Principal Display Panel (PDP) on all the maintenance and titration packs is not congruent with how the product is

expected to be prescribed, and is prone to confusion and wrong strength medication errors.

- For example, when looking at the titration blister pack PDP that states (b) (4) it is unclear that this packaging configuration intends to (b) (4)

We recommend you simplify the strength expression on the PDP in a manner that is consistent with how you expect the product to be prescribed. As you consider how best to display the strength on the PDP, you may wish to refer to approved products packaged in blister packs (e.g., Kisqali, Ingrezza).

2. The strength expression of the intended daily dose on the inside of the blister wallet labeling on some of the maintenance and titration packs is misleading and may lead to wrong dose medication errors.
   - For example, (b) (4)

     (b) (4)

   To minimize the risk for confusion, ensure that each row of tablets is labeled with its' corresponding tablet strength. Specifically, the following packs should be revised for clarity:

   (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xcopri received on November 21, 2018 from SK Life Science, Inc. .

Table 2. Relevant Product Information for Xcopri	
Initial Approval Date	N/A
Active Ingredient	cenobamate
Indication	Treatment of partial-onset seizures in adult patients
Route of Administration	Oral
Dosage Form	tablets
Strength	12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
Dose and Frequency	The recommended initial dose 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.
How Supplied	<u>Bottles</u> 50 mg: 30-count (NDC: 71699-050-30), (b) (4) 100 mg: 30-count (NDC: 71699-100-30), (b) (4) 150 mg: 30-count (NDC: 71699-150-30), (b) (4) 200 mg: 30-count (NDC: 71699-200-30), (b) (4) <u>28-Day Maintenance Pack:</u> (b) (4) 250 mg (50 mg + 200 mg) (NDC: 71699-102-56) 350 mg (150 mg + 200 mg) (NDC: 71699-103-56) <u>28-Day Titration Pack:</u> 12.5 mg + 25 mg (NDC: 71699-201-28) 50 mg + 100 mg (NDC: 71699-202-28) 150 mg + 200 mg (NDC: 71699-203-28) (b) (4)
Storage	Store tablets at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). (b) (4)
Container Closure	Bottles: High-density polyethylene (HDPE) white bottles (b) (4)

	Blisters: (b) (4) blister packages (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 22, 2019, we searched for previous DMEPA reviews relevant to this current review using the term, cenobamate. Our search did not identify any previous relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Xcopri labels and labeling submitted by SK Life Science, Inc. and received by the Agency on November 21, 2018.

- Commercial Container Labels

  Bottles

  - 30-Count: 50 mg, 100 mg, 150 mg, 200 mg

  (b) (4)

  28-Day Maintenance Pack:

  (b) (4)

  - 250 mg (50 mg + 200 mg)
  - 350 mg (150 mg + 200 mg)

  28-Day Titration Pack:

  - 12.5 mg + 25 mg
  - 50 mg + 100 mg
  - 150 mg + 200 mg

  (b) (4)

- Professional Sample Container Labels

  (b) (4)

- Medication Guide (Image not shown)
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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