CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210833Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210833
Priority or Standard	Standard
Submit Date(s)	10/31/2017
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Division/Office	DNP/ODE1
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	August 3, 2018
Established/Proper Name	Clobazam
(Proposed) Trade Name	Sympazan
Applicant	Aquestive Therapeutics
Dosage Form(s)	Oral film
Applicant Proposed Dosing Regimen(s)	5 mg to 40 mg (doses > 5 mg daily to be divided BID)
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	

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Glossary

AE	adverse event
AED	antiepileptic drug
ADR	adverse drug reaction
AR	adverse reaction
BMI	body mass index
BP	blood pressure
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COF	clobazam oral film
CRF	case report form
CRT	clinical review template
CSR	clinical study report
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
LGS	Lennox-Gastaut syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over-the-counter
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert

PK	pharmacokinetics
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RLD	reference listed drug
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens-Johnson Syndrome
SUDEP	sudden unexplained death in epilepsy
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
VPA	valproic acid

1. Executive Summary

1.1. Product Introduction

The applicant is planning to market clobazam oral film (COF, proposed proprietary name Sympazan) in the United States (US). Clobazam, the active ingredient in Sympazan, is a 1,5 benzodiazepine. Although the mechanism of action is not completely understood, it is thought to involve enhancement of GABAergic activity due to binding at the benzodiazepine site of the $GABA_A$ receptor.

COF contains clobazam, which is incorporated into [redacted] (b) (4) MonoSol Rx's PharmFilm® technology. The product is a white rectangular film. The applicant plans to market COF in 5 mg, 10 mg, and 20 mg strengths. The route of administration is gastrointestinal, after adherence to the lingual surface and dissolution.

Clobazam is currently approved for use in the US as Onfi tablets and oral suspension for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome.

The indication proposed by the sponsor is identical to that of the reference listed drug (RLD), Onfi, other than the trade name: "SYMPAZAN™ (clobazam) is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older."

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy was not assessed in the development program for COF, and the applicant is seeking no new indication. COF is a new formulation of an already approved drug, and the submission is a 505(b)(2) using Onfi (clobazam) tablets as the RLD. The clinical efficacy of clobazam for the proposed indication is based on the RLD as outlined in NDA 202067 and the determination of bioequivalence of COF to Onfi.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

As this application does not include efficacy data, the determination of benefit and risk depends significantly on the efficacy data from the RLD. The overall benefit-risk analysis of Sympazan (clobazam oral film) is therapeutically acceptable. Clobazam, marketed in the United States for patients with seizures associated with Lennox-Gastaut syndrome since 2011, has a well characterized safety profile. According to the Clinical Pharmacology reviewer for this application, Sympazan has been shown to be bioequivalent when compared to Onfi tablets. No new or unexpected adverse events were discovered in the course of the development program of Sympazan in healthy adults, and there are no clinical safety issues impeding the approval of the proposed product.

1.4. Patient Experience Data

As described below, the basis of this application is one "pivotal" bioequivalence study and one "pilot" bioequivalence study. No efficacy data are included. Patient experience data are not relevant to this application.

2. Therapeutic Context

2.1. Analysis of Condition

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy which presents during childhood. It is characterized by a triad of electro-clinical findings: multiple refractory seizure types, developmental delay and an interictal EEG pattern of diffuse, slow spike-wave complexes. LGS is considered a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities.

2.2. Analysis of Current Treatment Options

Seven drugs (including the RLD) are approved by the US Food and Drug Administration (FDA) for reduction of seizures in patients with LGS: cannabidiol, clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam (see Table 1 below).

Table 1: Summary of Treatments of Seizures in Patients with Lennox-Gastaut Syndrome

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for Lennox Gastaut Syndrome					
Cannabidiol	Treatment of seizures associated with LGS in patients ≥ 2 years of age	2018	10-20 mg/kg/day PO daily (divided BID)	Statistically significant reduction in median percent reduction from baseline (per 28 days) in drop seizure frequency in 2 studies 10 mg/kg/day: p<0.01 20 mg/kg/day: p<0.01 and p=0.01	Hepatocellular injury, somnolence and sedation, hypersensitivity reactions, decreased appetite and weight loss, diarrhea, decreased hemoglobin and hematocrit, and rash
Clobazam (RLD)	**Adjunctive treatment of seizures associated with LGS in patients ≥ 2 years of age**	**2011**	**Patients ≤30 kg: 5-20 mg PO daily (divided BID) Patients >30 kg: 20-40 mg/day PO (divided BID)**	**Statistically significant reduction in mean percent reduction from baseline in weekly drop seizure frequency: Low dose: p<0.05 Med dose: (p<0.01) High dose: (p<0.01)**	**Somnolence/sedation, withdrawal symptoms, skin reactions (Stevens-Johnson Syndrome [SJS], toxic epidermal necrolysis [TEN])**

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Rufinamide	adjunctive treatment of seizures associated with LGS in pediatric patients 1 year of age and older, and in adults	2008	45 mg/kg per day, divided BID, maximum 3200 mg per day	• Median percent change in total seizure frequency per 28 days (p=0.0015) • Median percent change in tonic-atonic seizure frequency per 28 days (p<0.0001) • Improvement in Seizure Severity Rating from Global Evaluation (p=0.0041)	Shortening of the QT interval (unknown clinical risk) Somnolence or fatigue, and coordination abnormalities, dizziness, gait disturbances, and ataxia Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Leukopenia
Lamotrigine	adjunctive therapy for generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older:	Initial: 1994 LGS: 1998	> 12 years: 100-500 mg divided BID (depending on concomitant AEDs esp., VPA) ≤12 years: 1-15 mg/kg/day, divided BID depending on concomitant AEDs (esp. VPA)	• Median percentage reduction from baseline in major motor seizures (p<0.05) • Drop attacks and tonic-clonic seizures were "significantly reduced" by lamotrigine	Serious skin rashes (including SJS), greater in pediatric than adult patients DRESS Hepatic failure Blood dyscrasias: neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia Aseptic meningitis SUDEP and status epilepticus

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Topiramate	adjunctive therapy for patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome	Initial: 1996 LGS: 2001	Adults: 200-400 mg/day PO divided BID Pediatrics: 5 to 9 mg/kg/day PO divided BID	• Median percent reduction in drop attacks ($p<0.05$) • Parental global rating of seizure severity ($p<0.05$)	Acute Myopia and Secondary Angle Closure Glaucoma; Visual Field Defects; Metabolic Acidosis; Cognitive-related dysfunction; depression or mood problems; Fetal anomalies (cleft lip and/or cleft palate and small for gestational age); hyperammonemia with or without encephalopathy; nephrolithiasis;
Felbamate	adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome	Initial: 1993 LGS: ??	45 mg/kg/day PO QID	• Statistically significant reductions in total, atonic, and tonic-clonic seizures	Aplastic anemia; hepatic failure;
Clonazepam	useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant)	Initial: 1975 LGS: 1997?	Adults: maintenance dose dependent on response, max 20 mg/day PO (divided TID) Pediatric: infants/children (≤10 years or 30 kg) maintenance dose of 0.1 to 0.2 mg/kg PO divided TID	• N/A	CNS depression, withdrawal symptoms; Worsening of Seizures especially in patients with multiple seizure types;

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Clobazam was approved as ONFI tablets for marketing in the US on October 21, 2011 for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older. This approval was based on two randomized, placebo-controlled efficacy studies (one pivotal and one supportive) and an open-label follow-on safety study. No major post-marketing safety issues that have been identified. Six nonclinical PMRs were issued at the time of the initial approval, all of which have been fulfilled. ONFI oral suspension was approved on December 14, 2012.

Current identified safety concerns for clobazam include the following as per the most recent PBRER for Onfi:

Important identified risks	CNS Depressive Effect - Concomitant Use with Opioids and Other CNS Depressants Hypersensitivity Hypothermia Physical and Psychological Dependence Sedation/Somnolence SJS/TEN and Other Severe Cutaneous Reactions Suicidal Behavior and Ideation Withdrawal
Important potential risks	Blood Dyscrasias Drug Induced Liver Injury DRESS Osteoporosis SUDEP
Important missing information	Use in Patients with Hepatic Impairment Use in Patients with Severe Renal Impairment Use in Pediatric Patients < 2 Years of Age Use in Pregnancy

Source: 2017 PBRER for NDA-202067

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 129383 was submitted to DNP on September 23, 2016 for a study of the pharmacokinetics and safety of clobazam oral film in healthy adults (Study 1895). A May Proceed letter was issued on November 22, 2016. A Type B preIND meeting request was submitted on January 20, 2016, and the Division of Neurology Products (DNP) provided written responses to the

questions on March 19, 2016. These responses included study design recommendations, agreement with the proposed nonclinical study, acceptability of the proposed 505(b)(2) application, and stipulation of the necessity to include a minimum of 12 months stability data in the future NDA submission.

3.3. Foreign Regulatory Actions and Marketing History

Clobazam was first licensed on February 6, 1970 in Australia, which is considered the International Birth Date for clobazam. As of October 2017, marketing authorizations for clobazam have been granted in more than 80 countries worldwide for a variety of indications including for acute and chronic anxiety states and for adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant monotherapy. See Section 3.1 for general safety concerns. There are no reported safety concerns specific to markets outside the US.

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested.

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control reviewer.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

For a full assessment of the nonclinical findings, please see the reviews by Drs. Freed and Fisher. At the time of this review, no nonclinical issues had been identified that would preclude approval.

4.5. Clinical Pharmacology

Pharmacokinetic parameters were assessed in Studies 162018 and 1895 for the purpose of assessing bioequivalence between clobazam oral film and the RLD (Onfi tablet) and are briefly

summarized below. Please refer to the review from the Office of Clinical Pharmacology (OCP) for the full review of the clinical pharmacology data.

In Studies 162018 and 1895, the hypothesis of bioequivalence of the formulations would be accepted if the 90% geometric CI of the ratio of least-squares means of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} for clobazam were between 80.00% and 125.00%. In Study 162018, all 90% geometric CIs were within this range. Thus, the applicant concluded that Study 162018 met the bioequivalence criteria for COF 20 mg and COF 10 mg. Additionally, comparisons between 10- and 20-mg doses of the study drug were within the range of 80.00% to 125.00%, leading to the conclusion that absorption (AUC and Cmax) is dose-proportional from 10 mg to 20 mg under fasting conditions.

Results of Study 1895 did not demonstrate clear bioequivalence between the formulations. The results revealed that peak absorption of COF was 10-12% higher compared to Onfi based on ratios for C_{max}. and that the extent of absorption of COF was approximately 8-9% greater than that of Onfi, based on ratios for AUC_{0-t} and AUC_{0-inf}. The 90% CIs for the ratios of the geometric means of AUC_{0-t} and AUC_{0-inf} were between 80.00% and 125.00% for both doses; however, the upper limit of the 90% CI for the Cmax ratio was greater than 125% at both dose levels (132.34% for 10 mg and 126.98% for 20 mg). The applicant posited that the higher 90% CIs may have been due to the small number of subjects and relatively high intra-subject variability.

Reviewer's Comments: Although the results of the PK analysis for Study 1895 did not demonstrate bioequivalence, these findings were complicated by small numbers of subjects in each study arm and relatively high intra-subject variability. The results of PK analyses in the larger study did demonstrate bioequivalence between COF and Onfi.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Clinical Studies in Healthy Subjects Contributing Safety Data

Study ID number	Trial Design	Regimen/ schedule/ route	Study Objectives	Treatment Duration/ Follow Up	No. of subjects enrolled
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
1895	Phase 1 pilot study: Randomized, open label, single dose, 3-period, 4-arm, crossover, fasting only	**Test drug:** COF 5 mg and COF 20 mg Dosage form: soluble film Route: Oral **RLD:** Onfi 10 mg and Onfi 20 mg Dosage form: tablet Route: oral	Primary: PK – compare BA COF vs RLD Secondary: safety and tolerability of COF	3 single doses administered each separated by ≥21-day washout period.	Safety population: n = 16 Received ≥1 dose COF: n = 15 Received ≥1 dose Onfi: n = 16 Age, years = 29-60
162018	Phase 1 "pivotal" BA/BE study: Randomized, open label, single dose, 4-period, 4-arm, crossover, fasting only ≥28-day washout period	**Test drug**: COF- 10 mg and COF- 20 mg Dosage form: soluble film Route: oral **RLD**: Onfi 10 mg and Onfi 20 mg Dosage form: tablet Route: oral	Primary: PK – compare BA COF vs RLD Secondary: safety and tolerability of COF	4 single doses administered each separated by ≥28-day washout period.	Safety population: n = 51 Received ≥1 dose COF: n = 50 Received ≥1 dose Onfi: n = 51 Age = 21–64 years

5.2. Review Strategy

A safety determination was made by evaluating the results from a "pivotal" randomized, open label, single dose, 4-period/4-arm, crossover study (Study 162018). Supporting safety data from a "pilot" open-label single dose 3-period/4-arm, crossover study (Study 1895) were also reviewed. This reviewer assessed safety by examining the source data provided by the applicant for Study 162018 and summary of safety data and case report forms for Study 1895.

In this 505(b)(2) application, the applicant is relying on prior safety and efficacy findings for the reference listed drug (RLD): ONFI® Oral Tablets (NDA 202067). The applicant provided clinical pharmacological data to demonstrate comparative bioavailability to the RLD. As no efficacy data were included in this application, Sections 6 and 7 are not applicable.

6. Review of Relevant Individual Trials Used to Support Efficacy

Not applicable

7. Integrated Review of Effectiveness

Not applicable

8. Review of Safety

8.1. Safety Review Approach

The safety data were generated from two open-label crossover studies that assessed the comparative bioavailability and safety of COF compared with the Onfi (the RLD). There were no placebo-controlled data for review. Analysis of the datasets were performed where possible.

8.2. Description of Clinical Trials Used to Support Safety

8.2.1. Study 162018

This was a randomized, open-label, crossover study comparing 20 mg and 10 mg doses of Clobazam OF and ONFI® tablets in healthy adults in fasted conditions. The purpose of the study was to demonstrate comparative bioavailability between the two clobazam formulations.

Objectives
Primary objective**:** *The primary objective of this pivotal study is to evaluate the comparative bioavailability of clobazam and N-desmethylclobazam from Clobazam Oral films 20and 10 mg (MonoSol Rx, LLC) and ONFI® Tablets 20 and 10 mg (Lundbeck, US) in healthy, non-smoking male and female volunteers under fasting conditions.*

Secondary objectives**:**
The secondary objective of this pivotal study is to assess the safety and tolerability of Clobazam Oral films (MonoSol Rx, LLC)

Study Design
This was a randomized, single dose, open-label, four-period/four-arm, crossover study with a planned sample size of 52 healthy subjects. Subjects were to receive a 20 mg clobazam tablet, a 20 mg clobazam OF, a 10 mg clobazam tablet, and a 10 mg clobazam OF; they were randomly assigned to 1 of 4 dosing sequences: ADBC, BACD, CBDA, DCAB (see Table 3 below). A 28-day washout period was planned between each dose.

Screening and Baseline Periods
Obtain informed consent, establish eligibility

Treatment Phase
The treatment phase consisted of 4 study periods (see Table 3).

Table 3: Description of Study Periods, Study 162018

Treatment Code	A	B	C	D
Product	Clobazam	ONFI (clobazam)	Clobazam	ONFI (clobazam)
Strength	20 mg	20 mg	10 mg	10 mg
Dosage form	Oral film	Tablet	Oral film	Tablet
Dose administered	1 x 20 mg	1 x 20 mg	1 x 10 mg	1 x 10 mg

Administration of clobazam OF is described in the protocol, as follows: *"The subject will be asked to move his/her tongue around the mouth (front and back part of gums, teeth and palate) 12 times to note any signs of oral irritation and/or any mouth, tongue or gum ulcer(s).*

Subsequently, a staff member centered the film directly on the top surface (dorsal aspect) of the subject's tongue and asked the subject to close his/her mouth in a natural way. The subject was asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film. Subjects were allowed to swallow saliva but not to chew, bite, or swallow the film...

"Visual inspection of the films was conducted by the study staff every minute (60 seconds) until either disintegration was noted or until the subject alerted the study staff regarding disintegration of the film by raising their hand. The disintegration time was checked for 5 minutes. If the film was not completely dissolved within 5 minutes, the subjects were allowed to swallow the medication."

Study Population
Healthy males or females, ages 18 to 64 years with BMI of 18.5 to 29.9 kg/m^2 were included. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and the usual clinical laboratory tests as well as negative screening of cotinine, ethanol and drugs of abuse in urine and negative pregnancy test (for female subjects).

The study included the following restrictions on prior and concomitant medications, food and beverages:

- No prescription drugs or OTC drugs beginning 14 days prior to dosing until the last blood draw of the final study period.
- No smoking or use of tobacco or nicotine-containing products from 6 months prior to dosing and throughout the entirety of the study.
- No use of marijuana or THC-containing products from 3 months prior to dosing and throughout the entirety of the study.
- No hormonal contraceptives, CNS depressant drugs, use of strong enzyme inducers/inhibitors, or foods/beverages containing grapefruit or pomelo beginning 30 days prior to dosing until the last blood draw of the final study period.
- No intake of caffeinated beverages or food, alcohol, or poppy seeds from 48 hours before dosing until after the last blood draw for each dose

The schedule of assessments is summarized in Table in Section (which is reproduced from the submission).

Table 4: Study Procedures and Evaluations, Study 162018

			Time points				
Procedure/Activity	**Screening**	**Each Period Check-in**	**Period 1**	**Period 2**	**Period 3**	**Period 4**	**Post-Study**
ICF	X						
Drugs of Abuse	X	X[a]					
Breath Alcohol	X	X[a]					
Cotinine	X	X[a]					
Serum hCG (females only)	X						
Urine hCG (females only)		X					X
BP	X		X[b]	X[b]	X[b]	X[b]	X
HR	X		X[b]	X[b]	X[b]	X[b]	X
RR	X						X
Temperature	X						X
Laboratory Testing	X						X
Medical History	X						
BMI	X						
ECG	X						
Inclusion/Exclusion Assessment	X						
Restrictions Compliance Check		X	X[c]	X[c]	X[c]	X[c]	
Physical Exam	X						X
Dosing			X	X	X	X	
PK Sampling			X[d]	X[d]	X[d]	X[d]	
Visual check at COF application site			X[f]	X[f]	X[f]	X[f]	
Adverse Event Reporting		X[e]	X[c]	X[c]	X[c]	X[c]	X
Meals		X	X	X	X	X	

[a] *On all subjects.*
[b] *Vital signs measurements (BP and HR) to be obtained at pre-dose and at 2 and 36 hours after dosing in each study period.*
[c] *Confirmed at each ambulatory blood draw, if applicable.*
[d] *PK sampling - pre-dose and at 0.333, 0.667, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 10.0, 12.0, 24.0, 28.0, 36.0, 48.0, 72.0, 96.0, 144, 240, 360 and 504 hours after dosing in each study period.*
[e] *Pre-dose conditions at Period 1 check-in.*
[f] *Visual inspection was performed at prior to study drug administration and approximately (within ±5 minutes) 0.167, 0.5, and 1 hour after complete dissolution of the COF to check for mucosal irritation at the application site.*
Source: Study 162018 CSR, Table 9.5.1-1

Assessments

Pharmacokinetic Assessments:

Blood samples for PK assessments were collected from pre-dose to 504 hours post-dose in all subjects.

Safety Assessments
All AEs and SAEs, laboratory values (hematology, blood chemistry, and urine values), vital signs, ECGs, and physical exams.

8.2.2. Study 1895

This was a randomized, open-label, crossover study comparing 20 mg and 5 mg doses of Clobazam OF and 20 mg and 10 mg ONFI® tablets in healthy, fasting adults. The purpose of the study was to demonstrate comparative bioavailability between the two clobazam formulations.

Objectives
Primary objective**:** *The primary objective of this pilot study was to evaluate the comparative bioavailability of clobazam and N-desmethylclobazam from Clobazam 5 mg & 20 mg Oral films (MonoSol Rx, LLC) and ONFI® 10 mg & 20 mg Tablets (Lundbeck, US) in healthy, non-smoking (for at least 6 months prior to first drug administration) male and female volunteers under fasting conditions.*

Secondary objectives**:**
The secondary objective was to assess the safety and tolerability of Clobazam 5 mg & 20 mg Oral films (MonoSol Rx, LLC).

Study Design
This was a randomized, single dose, open-label, four-period/four-arm, crossover study with a planned sample size of 52 healthy subjects. Subjects were to receive a 20 mg clobazam tablet, 20 mg clobazam OF, a 10 mg clobazam tablet, or 5 mg clobazam OF and were randomly assigned to 1 of 4 dosing sequences: ABD, CAB, BDC, or DCA (see Table 5 below). A 21-day washout period was planned between each dose.

Screening and Baseline Periods
Obtain informed consent, establish eligibility

Treatment Phase
The treatment phase consisted of 3 of 4 possible doses given in 3 study periods (see Table 5).

Table 5: Description of Study Periods, Study 1895

Treatment Code	A	B	C	D
Product	Clobazam	Clobazam	ONFI (clobazam)	ONFI (clobazam)
Strength	5 mg	20 mg	10 mg	20 mg
Dosage form	Oral film	Oral film	Tablet	Tablet

Administration of the clobazam OF is described as follows in the protocol: *"The subject will be asked to move his/her tongue around the mouth (front and back part of gums, teeth and palate) two times to note any signs of oral irritation and/or any mouth, tongue or gum ulcer(s). Just prior to drug administration, each subject will rinse his/her mouth for approximately 5 seconds with approximately 20 mL of room temperature water, and then will swallow this water. Subsequently, staff will center the film directly on the top surface (dorsal aspect) of the subject's tongue and ask the subject to close his/her mouth in a natural way. The subject will be asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film. Subjects will be allowed to swallow saliva but not to chew, bite, or swallow the film...*

"Visual inspection of the films will be conducted by the study staff every 2 minutes until either disintegration is noted or until the subject alerts the study staff to disintegration of the film by raising their hand. Subjects should refrain from talking until disintegration of the film is verified by study staff. If upon inspection, the film is not dissolved, staff will inform subjects to close their mouth in a natural way and continue to rub the film gently."

Study Population
Healthy males or females, ages 18 to 64 years with BMI of 18.5 to 29.9 kg/m^2 were included. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (ECG) and the usual clinical laboratory tests as well as negative screening of cotinine, ethanol and drugs of abuse in urine and negative pregnancy test (for female subjects).

The study included the following restrictions on prior and concomitant medications, food and beverages:

- No prescription drugs or OTC drugs beginning 14 days prior to dosing until the last blood draw of the final study period.
- No smoking or use of tobacco or nicotine-containing products from 6 months prior to dosing and throughout the entirety of the study.
- No use of marijuana or THC-containing products from 3 months prior to dosing and throughout the entirety of the study.
- No hormonal contraceptives, CNS depressant drugs, use of strong enzyme inducers/inhibitors, or foods/beverages containing grapefruit or pomelo beginning 30 days prior to dosing until the last blood draw of the final study period.
- No intake of caffeinated beverages or food, alcohol, or poppy seeds from 48 hours before dosing until after the last blood draw for each dose

The schedule of assessments is summarized in Table in Section (which is reproduced from the submission).

Table 6: Study Procedures and Evaluations, Study 1895

Procedure/Activity	Time points					
	Screening	Each Period Check-in	Period 1	Period 2	Period 3	Post-Study
Screening ICF	X					
ICF		X[a]				
Drugs of Abuse	X	X[b]				
Breath Alcohol	X	X[b]				
Cotinine	X	X[b]				
Serum hCG	X					
Urine hCG (females only)		X				
BP/HR/RR	X		X[c]	X[c]	X[c]	X
Temperature	X					X
Laboratory Testing	X					X
Medical History	X					
BMI	X					
ECG	X					
Inclusion/Exclusion Assessment	X					
Restrictions Compliance Check		X	X[d]	X[d]	X[d]	
Physical Exam	X					X
Dosing			X	X	X	
PK Sampling			X[e]	X[e]	X[e]	
Adverse Event Reporting		X[f]	X[d]	X[d]	X[d]	X
Visual oral inspection			X[g]	X[g]	X[g]	
Meals		X	X	X	X	

a- At Period 1 check-in only.
b- On all subjects.
c- Vital signs measurements (BP and HR) to be obtained at pre-dose and at 2 and 36 hours after dosing in each study period.
d- Confirmed at each ambulatory blood draw, if applicable.
e- PK sampling - pre-dose and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 28, 36, 48, 72, 96 and 144 hours after dosing in each study period.
f- Pre-dose conditions at Period 1 check-in.
g. Visual inspection will be performed at 10, 30, and 60 minutes after complete dissolution of the clobazam oral films to check for mucosal irritation at the application site.
Source: Study 1895, Protocol, pg. 29

Assessments

Pharmacokinetic Assessments:

Blood samples for PK assessments were collected from pre-dose to 144 hours post-dose in all subjects.

Safety Assessments
All AEs and SAEs, laboratory values (hematology, blood chemistry, and urine values), vital signs, ECGs, and physical exams.

8.3. Review of the Safety Database

8.3.1. Overall Exposure

All clinical safety data were generated in Studies 162018 and 1895. The data from these studies constitute the safety database and provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs. The safety database includes 67 subjects who were exposed to at least one dose of either COF or Onfi, as summarized in Table 7. All subjects (67/67) received at least one dose of Onfi, and 65/67 (97%) received at least one dose of COF.

Table 7: Total Safety Population

Study Groups (all healthy volunteers)	Clobazam OF (n=65)	Onfi Tablets [RLD] (n=67)
Study 162018	50	51
Study 1895	15	16

Source: Summary of Clinical Safety (SCS)

Of the 51 subjects enrolled in Study 162018, 46 completed the study, and 45 completed all four treatments (one subject missed the second treatment but completed the other three treatments). Of the 16 subjects enrolled in Study 1895, 11 subjects completed the three treatment periods. Disposition of subjects from each study are summarized in Table 8 and Table 9, below.

Table 8: Disposition of Subjects in the Safety Dataset, Study 162018

Category	COF 20 mg (A)	ONFI 20 mg (B)	COF 10 mg (C)	ONFI 10 mg (D)	Overall
Enrolled, n					51
Dosed, n	46	49	49	49	51
Completed study, n					46
Completed all treatment periods, n					45
Number of subjects discontinued, n	0	1	2	2	5

Category	COF 20 mg (A)	ONFI 20 mg (B)	COF 10 mg (C)	ONFI 10 mg (D)	Overall
Primary reason for discontinuation, n (%)					
Adverse event	0	0	1 (50)	0	1 (20)
Withdrawal by subject	0	1 (100)	0	1 (50)	2 (40)
Other	0	0	1 (50)	1 (50)	2 (40)

Source: ISS, Table 3

Table 9: Disposition of Subjects in the Safety Dataset, Study 1895

Category	COF 20 mg (B)	ONFI 20 mg (D)	COF 5 mg (A)	ONFI 10 mg (C)	Overall
Enrolled, n					16
Dosed, n	11	12	8*	11	16
Completed all treatment periods, n					11
Number of subjects discontinued, n	0	1	0	0	1
Primary reason for discontinuation, n (%)					
Adverse event	0	0	0	0	0
Withdrawal by subject	0	1 (100)	0	0	1 (100)
Other	0	0	0	0	0

* Four subjects received a single dose of COF 5 mg and four subjects received two doses of COF 5 mg, due to "a dispensing error".
Source: ISS, Table 4

In Study 162018, one subject discontinued participation due to an adverse event (see Section 8.5.3 below). Two subjects withdrew consent for "personal reason", and one withdrew because of illness and one because of difficulty with blood draw. In Study 1895, one subject did not return after the first study visit (no reason given).

In both studies, overall exposure was similar between the tablet and OSF formulations. Of the 51 subjects enrolled in Study 162018, 51 received the tablet formulation, and 50 (98%) received the oral film, while all subjects in Study 1895 received Onfi and 15/16 (94%) had at least one dose of COF. Dose-related exposures were also similar in each study (Table 10). Four subjects received 10 mg COF instead of the planned 5 mg dose. This error did not impact the safety assessment.

Table 10: Drug Exposure: Number of Subjects per Dose Level

	Dose Level		
	5 mg	**10 mg**	**20 mg**
COF			
Study 162018	-	49	46
Study 1895	4*	4*	11
Total	4	53	57
Onfi			
Study 162018	-	49	49
Study 1895	-	11	12
Total		60	61

* Four subjects who were intended to receive 5 mg COF were unintentionally administered 10 mg COF, due to "a dispensing error".
Source: ISS, Table 7

8.3.2. Relevant characteristics of the safety population:

Both studies enrolled healthy volunteers, using the same eligibility criteria. Overall demographics of the two studies were similar, as is seen in Table 11 below). The mean age for Study 162018 was 43.4 and was 46 in Study 1895. About half of the subjects in each study were women (49% and 56% in Studies 162018 and 1895, respectively). The majority of subjects were white (84% and 56% in Studies 162018 and 1895, respectively)

Table 11: Subject Demographics

Category	**Study 162018 N = 51**	**Study 1895 N = 16**
Age (years)		
Mean (SD)	43.4 (11.5)	46 (11)
Age groups (years) n (%)		
18–40	23 (45.1)	4 25)
41–64	28 (54.9)	12 (75)
Sex, n (%)		
Female	25 (49.0)	9 (56)
Male	26 (51.0)	7 (44)
Ethnicity, n (%)		
Not Hispanic/Latino	3 (5.9)	12 (75)
Hispanic/Latino	48 (94.1)	4 (25)
Race, n (%)		
White	43 (84.3)	4 (25)
Black	8 (15.7)	4 (25)
Asian	0	3 (18.75)

Category	Study 162018 N = 51	Study 1895 N = 16
Pacific Islander	0	0
Native American	0	1 (6.25)
BMI (kg/m2)		
Mean (SD)	26.1 (2.65)	25.9 (2.4)

Source: ISS, Table 6

8.3.3. Adequacy of the safety database

Based on the characteristics in Table 3, the development program is deemed to be generally adequate, especially since the sponsor is relying on the RLD for efficacy and controlled safety data.

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

The sponsor did not provide analyzable datasets for Study 1895, as the study was initiated on October 2, 2015, which was prior to December 17, 2016, thus allowing for legacy data submission. The lack of analyzable datasets for Study 1895 did not materially impact the safety review, as the number of subjects was small (n=16), and no significant safety findings were identified.

8.4.2. Categorization of Adverse Events

Adverse events were defined in the protocols of Study 162018 as *"any untoward medical occurrence (including* CS [clinically significant] *vital signs measurements or laboratory results) or worsening of a pre-existing condition in a subject administered a pharmaceutical product during the course of the study"*, regardless of the relationship to the study drug.

For the purpose of the safety analysis, treatment emergent adverse event (TEAEs) were defined as *"adverse events (AEs) that occurred on or after the date and time of study drug administration, or those that first occurred pre-dose but worsened in frequency or severity after study drug administration. TEAEs were attributed to the most recent study drug taken. A TEAE with a start date and time during the wash-out period (ending at the time of study drug administration) was attributed to the study drug taken during the previous treatment period."*

A serious adverse event was defined in the study protocols as *any untoward medical occurrence that at any dose:*

- *Resulted in death;*
- *Were life-threatening;*

- *Required in-patient hospitalization or prolongation of existing hospitalization;*
- *Resulted in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions);*
- *Was a congenital anomaly or birth defect;*
- *Was an important medical event that could jeopardize the subject or required intervention to prevent one of the other outcomes listed above (according to medical judgment of the PI).*

AEs were collected from the date of informed consent for both trials and until the last follow-up visit. AEs were followed until resolution or 30 days after the last follow-up visit, whichever came first. For each study, AEs were originally coded or were recoded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 for Study 162018. The version of MedDRA used in Study 1895 was not identified in the protocol or CSR.

8.4.3. Routine Clinical Tests

In Studies 162018 and 1895, clinical lab data were collected at screening and at the post-study visit. A serum pregnancy test was performed on women of child-bearing age at screening, and urine pregnancy tests were performed at check in prior to administration of the drug.

Clinical laboratory tests in both studies consisted of

- Hematology: Hemoglobin, Hematocrit, RBC, Platelet count, WBC and differential, Peripheral blood smear [if needed];
- Serum Chemistry/Hepatic Enzymes: Glucose, Calcium, Sodium, Chloride, Albumin, Protein, Bilirubin, Lactate Dehydrogenase, AST, ALT, Potassium, Alkaline Phosphatase, BUN, Uric Acid, Creatinine, Creatine Kinase);
- Urinalysis

Tests performed at screening only:

- Serology (HIV, Hepatitis B surface antigen, Hepatitis C antibody),
- breath alcohol test, urine cotinine, serum hCG, Urine Tests for Drugs of Abuse (marijuana, amphetamines, methamphetamines, phencyclidine, barbiturates, cocaine, opiates, benzodiazepines tetrahydrocannabinol, MDMA, and methadone).

Vital signs, ECGs, and physical and oral examinations were performed/collected during both studies.

8.5. Safety Results

8.5.1. Deaths

No deaths were reported in either study.

8.5.2. Serious Adverse Events

No serious adverse events were reported in either study.

8.5.3. Dropouts and/or Discontinuations Due to Adverse Effects

One subject discontinued participation due to a TEAE. Subject (b) (6) from Study 162018 was a 57-year-old male, who developed elevated blood pressure and heart rate. At his screening visit (b) (6) (b) (6) his blood pressure was 133/86 mm Hg and heart rate was 71 bpm. At his pre-dose assessment for Period 1 (b) (6) his BP was 151/86 mm Hg and HR was 105 bpm. Two hours after receiving Onfi 20 mg, his BP and HR had increased to 147/91 mm Hg and 104 bpm, respectively, but no clinical symptoms were reported. He missed the Period 2 visit (COF 20 mg). On (b) (6) (Period 3), his pre-dose BP was 157/92 mm Hg and HR was 114 bpm. Two hours after receiving COF 10 mg, his BP and HR had decreased to 126/81 mm Hg and 76 bpm. His Period 4 (b) (6) pre-dose BP and HR measurements were 153/92 mm Hg and 110 bpm, and again he was asymptomatic. Repeat measurements were 162/89 mm Hg and 119 bpm 1 hour later and 150/90 mm Hg and heart rate was 110 bpm 2 hours later. Due to the persistent elevated BP and HR, the subject was not dosed in Period 4 and was withdrawn from the study. The TEAE "blood pressure increased" was judged as mild and "heart rate increased" was judged as moderate. These TEAEs were considered by the investigator to be unlikely to be related to the study medication.

Reviewer's Comments: No serious or severe AEs were reported in either study. As noted above, one subject in Study 162018 discontinued participation due to an adverse event (hypertension and elevated heart rate), but the relationship of the study drug to this AE is unclear, as the subject's BP and HR were similarly elevated at baseline.

8.5.4. Significant Adverse Events

Irritation or injury to the oral cavity were considered to be AEs of special interest, and assessment of each subject's oral cavity was conducted before application, and at 10, 30, and 60 minutes after complete disintegration / dissolution of the COF in each study. During these inspections, no mucosal irritation or notable post-dose abnormalities were observed at the administration site after COF administration (COF 10 mg and 20 mg in Study 162018; COF 5 mg and 20 mg in Study 1895). However, one subject in Study 162018 (Subject (b) (6)) reported transient paresthesia of the tongue, which was documented as an AE deemed probably related to the study drug. This subject reported tongue numbness beginning shortly after administration of the COF 20 mg dose, and lasting for ~20 minutes. The AE was coded as mild and completely resolved.

There were no reported cases of allergic reaction (including rash and hypersensitivity), suicidality, or drug induced liver injury.

Reviewer's Comments: No AESIs were reported, other than one subject who developed transient oral paresthesia after administration of the COF 20 mg dose. This was considered possibly due to the study drug. No oral irritation or injury was reported.

8.5.5. Treatment Emergent Adverse Events and Adverse Reactions

Due to the lack of analyzable datasets for Study 1895, the safety analyses are not pooled and will be reported separately for each study.

Study 162018

A total of 106 TEAEs were reported by 34 (66.7%) of the 51 subjects who received at least one dose of study medication (safety population). Five AEs were reported in subjects prior to administration of the first study drug dose and are not included in the safety analyses. A higher number of TEAEs was observed following dosing with COF when compared with Onfi (clobazam) tablets for both dose level. Of the 106 TEAEs, 34 occurred in 45.7% of subjects after receiving COF 20 mg (A), 28 TEAEs in 40.8% of subjects after receiving ONFI 20 mg (B), 24 TEAEs in 30.6% of subjects after receiving COF 10 mg (C), and 20 TEAEs in 26.5% of subjects after receiving ONFI 10 mg (D).

As seen in Table 12 below, somnolence was the most common TEAE reported overall (43.1%). It was the most frequent TEAE in all groups except Onfi 10 mg. Other TEAEs that occurred in ≥5% of subjects overall were headache (27.5%), dizziness (11.8%), vomiting (7.8%), and diarrhea (5.9%). Somnolence, headache, dizziness, vomiting, and diarrhea were reported in the clinical trials for Onfi. None of the TEAEs reported in Study 162018 are of specific clinical concern.

None of the TEAEs were reported as severe. Eighty-eight (83%) were considered mild and 18 (17%) were considered moderate. No notable difference was observed with respect to TEAE severity among the treatment groups.

Table 12: All TEAEs, Study 162018

AE (Preferred Terms)	COF 20 mg (N=46)		Onfi 20 mg (N=49)		COF 10 mg (N=49)		Onfi 10 mg (N=49)		Overall (N=51)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All TEAEs	**21**	**(45.7)**	**20**	**(40.8)**	**15**	**(30.6)**	**13**	**(26.5)**	**34**	**(66.7)**
Somnolence	15	(32.6)	14	(28.6)	9	(18)	5	(10)	22	(43.1)
Headache	8	(17.4)	0	(0)	4	(8.2)	6	(12.2)	14	(27.5)
Dizziness	2	(4.3)	3	(6.1)	1	(2)	1	(2)	7	(11.8)
Vomiting	0	(0)	0	(0)	1	(2)	3	(6.1)	4	(7.8)
Diarrhea	0	(0)	2	(4.1)	1	(2)	0	(0)	3	(5.9)
Influenza like illness	0	(0)	0	(0)	0	(0)	2	(4.1)	2	(3.9)
Nausea	0	(0)	0	(0)	1	(2)	1	(2)	2	(3.9)
Abdominal Pain upper	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Blood creatine phosphokinase increased	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Blood glucose increased	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Blood pressure increased	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)
Catheter site hemorrhage	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Catheter site pain	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Catheter site swelling	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Constipation	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)
Decreased appetite	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Eosinophil count increased	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Glucose urine present	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Hemoglobin decreased	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)
Heart rate increased	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)
Joint injury	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Nasal congestion	0	(0)	0	(0)	1	(2)	0	(0)	1	(2)
Paresthesia oral	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Presyncope	0	(0)	0	(0)	0	(0)	1	(2)	1	(2)
Rhinitis	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Rhinorrhea	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)
Vessel puncture site bruise	1	(2.2)	0	(0)	0	(0)	0	(0)	1	(2)
Vessel puncture site hemorrhage	0	(0)	1	(2)	0	(0)	0	(0)	1	(2)

Source: FDA Clinical Reviewer (JMP). TEAEs in red occurred in ≥3% of subjects.

Reviewer's Comments: In general, the TEAEs reported in Study 162018 were consistent with adverse drug reactions (ADRs) included in the label for Onfi and/or were reported in the controlled clinical trials. Although the incidence of TEAEs was greater in the COF groups as compared to the Onfi groups, these differences were not significant enough to allow for any conclusions to be drawn.

Study 1895

Thirteen (81.2%) of the 16 subjects who received at least one dose of clobazam reported 22 TEAEs during Study 1895 (safety population). None of the TEAEs were serious, and all events were considered mild. As seen in Table 13 below, there was no pattern to the overall TEAEs with respect to dose or formulation, though any conclusions are complicated by small numbers of subjects in each dose group. As in Study 162018, somnolence was the TEAE that occurred most frequently (11/16, 68.8%). Headache occurred in 2 subjects (12.5%). The other 4 TEAEs occurred in only one subject each.

Table 13: All TEAEs, Study 1895

MedDRA Preferred Term	COF 20 mg (B) N=11		Onfi 20 mg (D) N=12		COF 5 mg (A) N=8		Onfi 10 mg (C) N=11		Overall N=16	
	n	%	n	%	n	%	n	%	n	%
All TEAEs	**4**	**36.4**	**9**	**66.7**	**6**	**62.5**	**3**	**18.2**	**13**	**81.2**
Somnolence	4	36.4	7	58.3	4	50.0	1	9.1	11	68.8
Headache	0	0	1	8.3	1	12.5	0	0	2	12.5
Nausea	0	0	0	0	1	12.5	0	0	1	6.25
Chest pain	0	0	0	0	0	0	1	9.1	1	6.25
Feeling hot	0	0	1	8.3	0	0	0	0	1	6.25
Cough	0	0	0	0	0	0	1	9.1	1	6.25

Reviewer's Comments: In general, the TEAEs reported in Study 1895 were consistent with ADRs included in the label for Onfi and/or were reported in the controlled clinical trials. No safety issues have been identified in the analysis of the adverse events of Study 1895.

8.5.6. Laboratory Findings

As with the AE analysis, Studies 162018 and 1895 are not pooled for analysis of laboratory values.

Laboratory testing was performed at screening and at a post study visit.

Study 162018

The mean values for all laboratory parameters were within the normal range at each timepoint and were generally unchanged when compared to baseline. The shift analyses revealed no clinically significant shift for any parameter. When individual results in individual subjects are considered, abnormalities were reported for some parameters for some subjects; however, only 5 changes were considered clinically significant and reported as TEAEs (Table 14). All were deemed mild and were not associated with any clinical findings. These abnormalities all were

reported as "Not Resolved". The applicant noted that these subjects were all sent a letter referring them to their primary physician for follow-up. Of note, one of the abnormalities (glucose in urine) was present at baseline.

Table 14: Lab value abnormalities coded as TEAEs, Study 162018

Subj. No.	Treatment sequence	Adverse Event (PT)	Test Normal Range	Baseline Result	Clinically Significant Result	Repeat	Resolution
(b) (6)	DCAB	Glucose urine present	Negative	3+	3+	3+	NOT RESOLVED
		Blood glucose increased	65-99 mg/dL	86	144	130	NOT RESOLVED
	ADBC	Hemoglobin decreased	11.1-15.9 g/dL	12.8	10.9	10.7	NOT RESOLVED
	BACD	Blood creatine phosphokinase increased	24-204 U/L	405	632	Not available	NOT RESOLVED
	DCAB	Eosinophil count increased	0-0.4 $x10^9$/L	0.3	1.0	1.4; 0.8	NOT RESOLVED

Study 1895

No baseline or post-study laboratory results outside of normal range that were reported as Clinically Significant by the Investigator. Individual laboratory values were not provided for review.

Reviewer's Comments: No significant laboratory abnormalities were identified.

8.5.7. Vital Signs

In both COF studies, all individual measurements of vital signs were within normal range, returned to normal after repeated measurements, or were deemed not clinically significant by the investigator, other than the elevated BP and HR which led to discontinuation of subject (b) (6) in Study 162018 (see Section 8.5.3). The mean values for all time points and all parameters were within normal range. No notable differences in mean values or changes from baseline were observed for measurements of vital signs over time, and no significant differences were observed between results of subjects. A few subjects had mildly abnormal vital signs, but none of the abnormalities were considered TEAEs other than Subj (b) (6). These abnormal values generally occurred in subjects with low or high baseline values that were not notably different from the post-dose results.

Reviewer's Comments: No safety signal related to vital signs was identified.

8.5.8. Electrocardiograms (ECGs)

ECGs were assessed during Study 162018 at screening only. ECGs were not performed during Study 1895.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Safety in the Postmarket Setting

8.7.1. Safety Concerns Identified Through Postmarket Experience

Clobazam OF is not approved for use, so there are no available postmarket data specific to this formulation. The 120-day safety update identified no new safety issues.

8.7.2. Expectations on Safety in the Postmarket Setting

I expect the patterns in adverse reactions in the postmarketing data will be similar to the patterns observed in the pre-marketing data.

8.7.3. Additional Safety Issues From Other Disciplines

None

8.8. Integrated Assessment of Safety

This review summarizes the safety data collected from 65 healthy subjects exposed to clobazam oral film in two bioequivalence studies. The clinical safety tests conducted in the studies were appropriate and capable of identifying major safety signals. Overall, the safety findings from this submission are consistent with data from the original NDA submission for clobazam tablets (Onfi). No new safety signals were identified in either Study 162018 or Study 1895.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not considered necessary.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The labeling has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS was deemed unnecessary.

12. Postmarketing Requirements and Commitments

The necessity of post-marketing requirements or commitments has not been determined at the time of this review.

13. Appendices

13.1. References

See footnotes throughout the review.

Financial Disclosure

Covered Clinical Study (Name and/or Number): 1895, 162018

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE B GETZOFF
08/03/2018

PHILIP H SHERIDAN
08/30/2018