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Established Name Clobazam
(Proposed) Trade Name Onfi
Therapeutic Class Anticonvulsant
Applicant Lundbeck Inc.

Formulation(s) Tablet 5 mg., 10 mg., 20 mg.
Dosing Regimen BID
Indication(s) Treatment of Lennox Gastaut
Syndrome
Intended Population(s) Patients \geq 2 years of age with
Lennox Gastaut Syndrome

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients age 2 years of age and above.

1.2 Risk Benefit Assessment

Lennox-Gastaut syndrome (LGS) is a severe childhood epileptic encephalopathy characterized by a slow spike and wave electroencephalogram (EEG), multiple seizure types, and usually an abnormal developmental state and behavioral disturbances. Recurrent episodes of status epilepticus may occur. Onset of LGS, as determined by the appearance of the characteristic seizures, generally occurs between 3 and 8 years of age, with peak occurrence between 3 and 5 years. Most patients continue to have refractory epilepsy and continued neurocognitive impairment that persist into adulthood.

Lennox-Gastaut syndrome is characterized by multiple seizure types, predominantly of the tonic, atonic, and atypical absence variety. Pharmaceutical agents that show improvement in the most debilitating variety of seizures, drop seizures, are particularly desirable in this population. A drop seizure is defined as a drop attack or spell involving the entire body, trunk, or head that leads to a fall, injury, slumping in chair, or head hitting surface or that could have led to a fall or injury, depending on the position of the patient at the time of seizure onset. These drop attacks lead to significant head trauma and necessitate the wearing of a protective helmet. Drop attacks, which may occur as a result of tonic, atonic or myoclonic seizures, are particularly disabling to patients with LGS, and indeed the falls pose a safety hazard to patients. These drop attacks occur in about 56% of patients who have slow spike and wave on EEG.

Lennox-Gastaut syndrome poses a significant treatment challenge. No single anti-epileptic drug (AED) provides satisfactory relief for all or most subjects with LGS, and a combination of treatments is often required. Even with combination therapy, many LGS subjects show resistance to treatment. Adjunctive therapy with newer anticonvulsant medications has demonstrated efficacy for some subjects, although polytherapy and high medication doses are often associated with unfavorable adverse event profiles. Currently, five antiepileptic drugs (AEDs) (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide) have demonstrated clinical efficacy and are approved by the Agency for the treatment of LGS. Despite the availability of these approved treatments, many patients with LGS continue to be

refractory to treatment. More effective and better tolerated treatment options are needed for this population.

The efficacy studies reviewed demonstrate that clobazam at tolerable doses is effective in reducing the number of both intractable drop and non-drop seizures associated with LGS. It has been marketed for forty years in many other countries so its adverse event profile is known to be similar to other benzodiazepines, such as clonazepam which is already approved in the United States for adjunctive treatment of seizures associated with LGS. The efficacy appears to persist for most patients despite the known tendency for patients to develop tolerance to benzodiazepines. Therefore, the benefits of approval of clobazam outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

None from clinical review.

1.4 Recommendations for Postmarket Requirements and Commitments

None from clinical review.

2 Introduction and Regulatory Background

2.1 Product Information

Clobazam is a 1,5–benzodiazepine approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide. It is not currently approved in the United States for any indication.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, five AEDs (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide) have demonstrated clinical efficacy and are approved by the Agency for the treatment of LGS. Despite the availability of these approved treatments, many subjects with LGS continue to be refractory to treatment. More effective and better tolerated treatment options are needed for this population of medically intractable epilepsy subjects.

Table 1 Alternative Therapies for LGS

Drug name	Drug class
clonazepam	benzodiazepine
felbamate	dicarbamate
lamotrigine	phenyltriazine
topiramate	sulfamate
rufinamide	triazole

2.3 Availability of Proposed Active Ingredient in the United States

Clobazam is not currently marketed in the United States for any indication.

2.4 Important Safety Issues With Consideration to Related Drugs

Intravenous benzodiazepines used acutely for status epilepticus may cause respiratory and cardiovascular depression. With chronic oral use, the benzodiazepines produce sedation, drowsiness, lightheadedness, ataxia, cognitive slowing, headache, vertigo, and gastrointestinal symptoms. There is also a risk for the development of tolerance to efficacious effect. Abrupt withdrawal benzodiazepines may cause seizures, insomnia, psychiatric symptoms, or delirium tremens.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Clobazam was first approved in 1970 in Australia (international birth date) and has also been approved for the treatment of anxiety and/or the adjunctive treatment of epilepsy in over 100 countries.

In the U.S., an IND was filed on 25 May 2005 by Lundbeck Inc. (Lundbeck) (formerly Ovation Pharmaceuticals); the company was notified by the Division of Neurology Products on 24 June 2005 that clinical studies with clobazam under IND 70,125 could proceed. A Type B, End of Phase 2 (EOP2) meeting was held with the Division on 09 May 2007 to discuss the results obtained from the completed Phase 2 study, OV -1002, and to discuss planning for the pivotal Phase 3 study (OV-1012) and preparation for filing a U.S. NDA.

During the EOP2 meeting, the Agency expressed concern about the potential for patients developing tolerance to benzodiazepines, thus leading to a lack of long-term efficacy. To address this possibility, the Maintenance Phase for the pivotal Phase 3 study (OV-1012) was lengthened from 8 to 12 weeks.

Lennox-Gastaut syndrome (LGS) is estimated to represent 1 % to 2% of all childhood epilepsy cases. Therefore, LGS affects fewer than 200,000 people in the United States (US), and in accordance with Code of Federal Regulations (CFR) 21CFR 316.20, qualifies as an orphan indication. On 24 August 2007, Lundbeck submitted an Orphan Drug Application requesting Orphan Drug Designation for clobazam. Orphan drug designation was awarded on 18 December 2007.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The studies have been conducted and reported with adequate quality and integrity.

3.2 Compliance with Good Clinical Practices

The studies submitted for review are compliant with Good Clinical Practices.

3.3 Financial Disclosures

The two clobazam clinical efficacy studies which support the proposed indication of adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) are the pivotal study OV-1012 and the supportive study OV-1002.

Studies OV-1012 and OV-1002 were sponsored by Lundbeck Inc. (formerly Ovation Pharmaceuticals), and financial disclosure and certification were collected from participating clinical investigators.

Study OV-1012 or OV-1002 clinical investigators with financial interests requiring disclosure are shown in the Sponsor's table reproduced below.

The Sponsor does not believe that this disclosure of financial interests biases the OV-1012 or OV-1002 study results.

Table 2 Clinical Investigators with Financial Interests Requiring Disclosure

Study No.	Site No.	Investigator Name	Patients Enrolled	Disclosable Financial Information
OV-1012	(b) (6)	(b) (6)	(b) (6)	(b) (6) received individual payments from Lundbeck that totaled between \$25,000 and \$50,000. All payments were for (b) (6) participation in (b) (6) (b) (6) promotional activities.
OV-1002				(b) (6) received individual payments from Lundbeck that totaled between \$25,000 and \$50,000. Payments were for (b) (6) participation at (b) (6) (b) (6) annual meetings and for (b) (6) consulting services in support of (b) (6) clinical protocol development and OV-1012 Executive Study Management Committee.
OV-1002				Via a signed contract between Lundbeck and (b) (6) (b) (6) Lundbeck will pay 5% of (b) (6) sales to a non-profit educational fund. Twenty percent of this fund will go to studies sponsored by (b) (6) Upon (b) (6) death, 1% of sales will go to (b) (6) (b) (6) has provided details of (b) (6) disclosable financial arrangements with Lundbeck (Attachment 1).
OV-1002				(b) (6) received individual payments from Lundbeck that totaled between \$25,000 and \$50,000. Payments were for (b) (6) participation in the (b) (6) (b) (6) in addition to various advisory boards related to protocol development and launch.
OV-1002				(b) (6) received individual payments from Lundbeck that totaled between \$50,000 and \$75,000. Payments were for (b) (6) participation in the (b) (6) (b) (6) in addition to various advisory boards related to protocol development and launch.

The other principal investigators had no financial interests to disclose.

Reviewer Note:

The potential bias that these 5 investigators might have introduced to the studies depends on the number of patients that their sites enrolled in the two studies.

Supportive Study OV-1002

The investigator who would appear to have a significant ongoing financial interest (b) (4) (b) (6)

(b) (6) contributed (b) (6) to Study OV-1002 and (b) (6) patients to the pivotal study OV-1012. The other 4 investigators who enrolled the other (b) (6) (b) (6) from these 5 sites have provided professional services to Lundbeck with remuneration in the evaluation and promotion of (b) (6) in the past but report no ongoing financial interests. (b) (6) is a possible exception since

she also

(b) (6)

Study OV-1002 (15 sites) enrolled 68 patients of which 58 completed. These five investigators enrolled 16 patients in OV-1002. If all 16 patients were completers, the percentage of patients from these 5 sites would be about 27%. Assuming a worst case scenario, the question arises as to whether the exclusion of these patients would change the outcome of this supportive study. However, the Agency performed a re-analysis of the primary outcome of Study OV-1002 without the patients from the 5 sites in question and found that the superiority of the high dose arm compared to low dose arm remained very significant.

Pivotal Study OV-1012

The four investigators at 4 sites reporting financial interests have provided professional services to Lundbeck with remuneration in the evaluation and promotion of (b) (6) in the past but report no ongoing financial interests. (b) (6)

(b) (6)

Study OV-1012 (51 sites) enrolled 238 patients of which 177 completed the study. Four of the sites contributed a total of 16 patients to OV-1012. If all were completers, this would be about 9% of the patients. The Agency performed a re-analysis of the primary outcome of Study OV-1012 without the patients from the 4 sites in question. The medium and high dose arms were again found to be superior to placebo with high statistical significance. The low dose arm was no longer found to be significantly superior to placebo, possibly due to reduced statistical power after the exclusion of the 16 patients.

Conclusion:

The exclusion of all patients from the 5 sites where the investigators had declared financial interests in the Sponsor Lundbeck did not change the primary outcome of either the pivotal study or the supportive study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not applicable.

5 Sources of Clinical Data

The Sponsor presents two individual studies in support of efficacy: pivotal study OV-1012 and supportive study OV-1002

Tables of Studies/Clinical Trials

Table 3 Clinical Studies and Long-Term Study Supporting Efficacy

Efficacy Studies	Title
Pivotal Study OV-1012	Double-blind, Placebo-Controlled, Efficacy and Safety Study of Clobazam (0.25, 0.5, and 1.0 mg/kg/day) in Patients with Lennox-Gastaut Syndrome
Supportive Dose-Ranging Study OV-1002	Multicenter, randomized, double-blind, dose-ranging study designed to assess the safety and efficacy of clobazam as adjunctive therapy in subjects 2-30 years of age with Lennox-Gastaut Syndrome
Ongoing Long-term Extension Study OV-1004	Ongoing multicenter open-label uncontrolled extension study of subjects from OV-1002 and OV-1012 to assessing long-term safety and efficacy of clobazam as adjunctive therapy in subjects with Lennox-Gastaut Syndrome

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Table 4 Pivotal Study OV-1012 (Sponsor's ISE Table 1)

Table 1. Description of Double-blind Clinical Efficacy Studies

Study ID/ Type of Study/ Type of Report	Number of Study Centers (Locations)	Study Start Study Completion Enrollment Status Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Gender Male/Female Median Age (Range) Race	Inclusion Criteria	Primary Endpoint
OV-1012/ Efficacy and safety/ Full	51 primary investigative sites (US, Australia, Belarus, India, and Lithuania)	23 August 2007 - 21 December 2009 Complete 238 / 240	R, DB, placebo- control, parallel- group 4-week BL period, 3-week titration period, 12-week maintenance period, a 2- or 3-week taper period for subjects not continuing in OV-1004	Oral placebo Oral CLB: low dose: target dose of 0.25 mg/kg (maximum of 10 mg/day), medium dose: target dose of 0.5 mg/kg (maximum of 20 mg/day), or high dose: target dose of 1.0 mg/kg (maximum of 40 mg/day) Subjects were dosed twice daily.	Determine the efficacy of CLB in the reduction of drop seizures at 3 dose levels when compared to BL during 12 weeks maintenance dosing in subjects with LGS; determine the safety of CLB when administered for up to 18 weeks at 3 different dose levels in subjects with LGS	Placebo: 59 / 41 CLB dose: Low: 58 / 50 Medium: 62 / 45 High: 59 / 41	Up to 18 weeks of study drug	144 / 94 10.1 (2 - 54) years Caucasian: 147 Asian: 61 Other: 30	Subjects 2-60 years of age with a diagnosis of LGS, < 11 years of age at onset of LGS, weight ≥ 12.5 kg, ≥ 2 drop seizures per week during the 4-week BL period, been on ≥ 1 AED and on a stable dose for ≥ 4 weeks prior to screening (VNS and ketogenic diet were not considered AEDs), and not chronically on any benzodiazepines for a period of ≥ 30 days prior to screening.	Percent reduction in number of drop seizures (average per week) from the 4-week BL period compared to the 12-week maintenance period

AED = anti-epileptic drug; BL = baseline; CLB = clobazam; DB = double-blind; LGS = Lennox-Gastaut syndrome; R = randomized; US = United States; VNS = vagal nerve stimulator

Table 5 Supportive Study OV-1002 (Sponsor's ISE Table 1)

Table 1. Description of Double-blind Clinical Efficacy Studies (continued)

Study ID/ Type of Study/ Type of Report	Number of Study Centers (Locations)	Study Start Study Completion Enrollment Status Total Enrollment/ Enrollment Goal	Design Control Type	Study and Control Drugs Dose, Route, Regimen	Study Objective	# Subjects by Arm Entered/ Completed	Duration	Gender Male/Female Median Age (Range) Race	Inclusion Criteria	Primary Endpoint
OV-1002/ Efficacy and safety/ Full	15 (US)	05 October 2005 - 08 August 2006 Complete 68 / 60	R, DB, dose- ranging 4-week BL period, 3-week titration period, 4-week maintenance period, up to 3-week taper period for subjects not continuing in OV-1004	Oral CLB: low dose: target dose of 0.25 mg/kg (maximum of 10 mg/day) or high dose: target dose of 1.0 mg/kg (maximum of 40 mg/day) Subjects were dosed twice daily.	Determine the safety and efficacy of low- dose and high- dose CLB in the treatment of seizures that lead to drop attacks in subjects with LGS	Low dose: 32 / 28 High dose: 36 / 30	Up to 10 weeks of study drug	42 / 26 7.4 (2 - 26) years Caucasian: 59 Asian: 1 Other: 8	Subjects 2-30 years of age with a diagnosis of LGS, < 11 years of age at onset of LGS, weight ≥ 12.5 kg, ≥ 2 drop seizures per week during the 4-week BL period, been on ≥ 1 AED and on a stable dose for ≥ 4 weeks prior to screening (VNS and ketogenic diet were considered AEDs), and not chronically on any benzodiazepines for a period of ≥ 5 half-lives prior to study entry.	Percent reduction in number of drop seizures (average per week) from the 4-week BL period compared to the 4-week maintenance period

AED = anti-epileptic drug; BL = baseline; CLB = clobazam; DB = double-blind; LGS = Lennox-Gastaut syndrome; R = randomized; US = United States; VNS = vagal nerve stimulator

5.2 Review Strategy

I have reviewed the individual study reports (Study OV-1012, Study OV 1002, and Study OV-1004) and the integrated summary of efficacy for these efficacy studies. The safety data from these and other studies are being reviewed in a separate review by Dr Gerard Boehm.

5.3 Discussion of Individual Studies/Clinical Trials

The Sponsor presents two individual studies in support of efficacy: pivotal study OV-1012 and supportive study OV-1002. Study OV-1004 is an open-label follow-on study of patients who have participated in OV-1002 or OV-1012 which provides further safety information and an indication of long-term efficacy.

Pivotal Study for Efficacy Study OV-1012

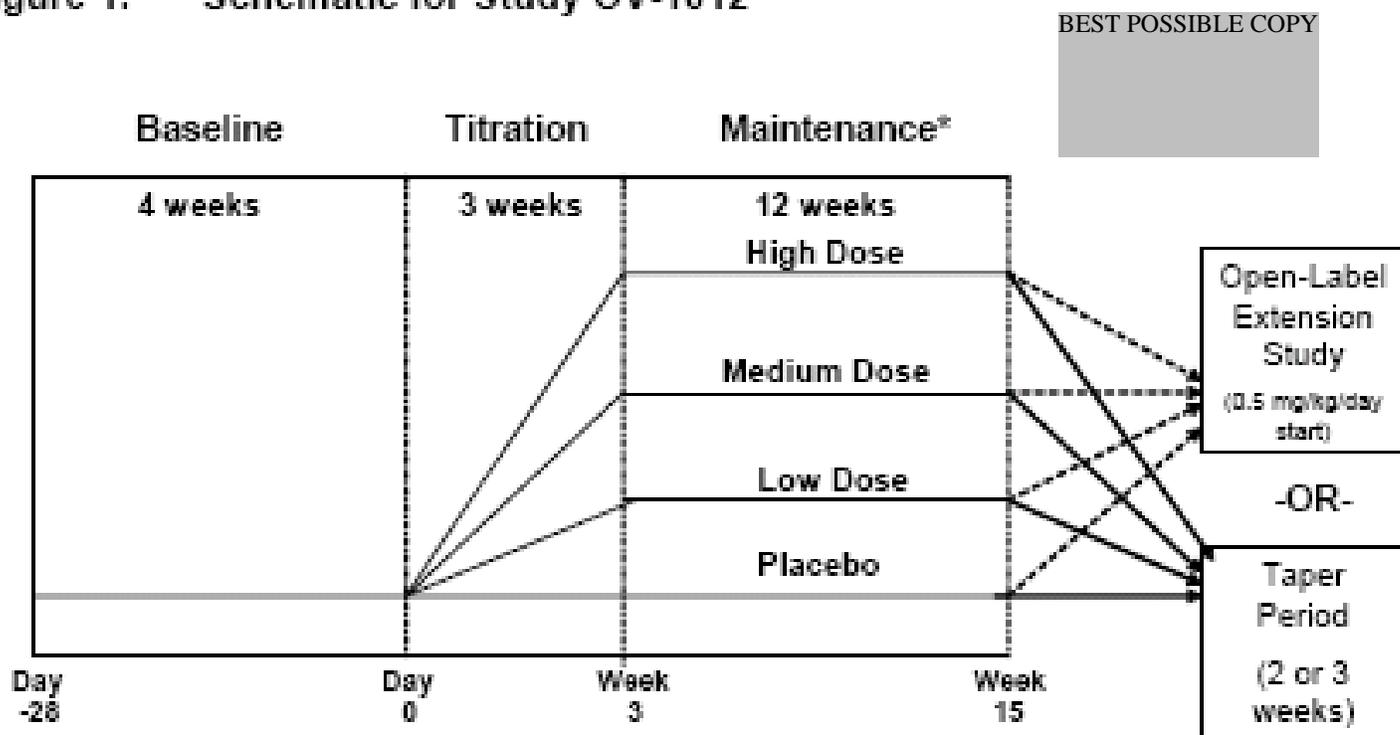
The Phase 3 pivotal efficacy study was entitled “Double-blind, Placebo-Controlled, Efficacy and Safety Study of Clobazam (0.25, 0.5, and 1.0 mg/kg/day) in Patients with Lennox-Gastaut Syndrome”.

Design:

Study OV-1012 was a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study designed to assess the efficacy and safety of clobazam as adjunctive therapy to a stable AED regimen in subjects 2 to 60 years of age with LGS. This study comprised a 4-week baseline period, a 3-week titration period, a 12-week maintenance period, and a 2- or 3-week taper period (depending upon the subject weight group) for subjects not continuing into the open-label extension study (OV-1004). The study schematic (Figure 1 from the sponsor)

Figure 1 Schematic for Study OV-1012 (Sponsor's ISE Figure 1)

Figure 1. Schematic for Study OV-1012



* Subjects not directly continuing into the open-label extension study tapered off study drug in a 2- or 3-week taper period, depending on weight group, with the final visit 1 week post last dose.

Reviewer Note:

The maintenance period of 12 weeks was longer than in most efficacy studies in order to ascertain if patients who initially responded to clobazam would develop a tolerance to its efficacious effects. The medical literature indicates that if tolerance is going to develop it will occur in most cases within 2-3 months of the patient's beginning clobazam therapy.

On Day -1, subjects were stratified into 1 of 2 prespecified weight groups (12.5 kg to \leq 30 kg and $>$ 30 kg) and randomly assigned to placebo or a low (target dose of 0.25 mg/kg [up to a maximum daily dose of 10 mg]), medium (0.5 mg/kg [up to a maximum daily dose of 20 mg]), or high (1.0 mg/kg [up to a maximum daily dose of 40 mg]) dose of clobazam.

During the 3-week titration period (office visits at Weeks 1, 2, and 3), subjects began taking either 5 mg or 10 mg clobazam daily or matching placebo in divided doses, increasing the dose every 7 days until the target dose was attained. The target dose was then administered for 12 weeks (maintenance period). Study medication was administered twice daily (BID) with doses in the morning and at bedtime; when the daily

dose could not be equally divided between the morning and evening dose, the higher dose was to be given in the evening. After the maintenance period, study medication was tapered over 2 to 3 weeks (depending upon the subject weight group, with heavier subjects having a 3-week taper) unless the subject continued into the open-label extension study (OV-1004).

At any time during the study, beginning with the first week of the titration period, if a subject developed any sign or symptom that represented difficulty tolerating study drug, the Investigator could have reduced the daily dosage by one 5 mg tablet. The minimum clobazam dose was 5 mg/day. In order to remain blinded, for subjects only on 5 mg per day, the reduction in medication was a placebo tablet, not clobazam. Subjects who could not tolerate the target dose or the decreased dose were discontinued from the study but may have been eligible to enter into the open-label extension study (OV-1004). If any subject was being considered for premature discontinuation, the Investigator was to contact the medical monitor for approval to enter that subject into the open-label extension study.

Subjects were allowed rescue therapy of 1 rescue per day with no more than a total of 4 days in 4 weeks (average of 1 rescue dose per week). If more rescue treatments were required, the subject was considered a treatment failure, discontinued from the study, and tapered off study drug or enrolled in the open-label extension study. Rescue treatment options could have included, but were not limited to, diazepam and lorazepam. Clobazam was not to be used as a rescue medication.

Seizures were to be recorded on a daily basis in seizure diaries by the parent/caregiver, with the assistance of the subject, if able. Seizure rates were calculated and summarized as weekly averages. Baseline seizure rates were calculated from the 4-week baseline period that preceded randomization. The weekly number of drop seizures during baseline was the number of drop seizures reported during baseline divided by the number of days recorded during baseline multiplied by 7. Similarly, the weekly number of drop seizures during maintenance was the number of drop seizures reported during maintenance divided by the number of days during maintenance multiplied by 7.

Inclusion/Exclusion criteria:

In order to qualify for the study, subjects had to have a diagnosis of LGS, including written documentation of having met EEG diagnostic criteria at some point in their history, and evidenced by more than one type of generalized seizure, including drop seizures (atonic, tonic, or myoclonic) for at least 6 months. Subjects must also have experienced at least 2 drop seizures per week during the baseline period and been taking a stable regimen of 1 to 3 AEDs for at least 30 days prior to screening. The only prohibited AEDs as part of the stable regimen were benzodiazepines, except as rescue medications.

Outcome Measures:

The primary efficacy variable was the percent reduction in drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period. A positive value for the percent reduction in drop seizures indicated a reduction in the number of drop seizures.

The key secondary and additional efficacy variables include:

- percent reduction in the number of drop seizures (average per week) from baseline compared to the first 4 weeks/last 4 weeks of the maintenance period
- percent responders, defined as those with $\geq 25\%$ / $\geq 50\%$ / $\geq 75\%$ /100% reduction in drop seizures (average per week) from baseline compared to the maintenance period
- percent responders, defined as those with $\geq 25\%$ / $\geq 50\%$ / $\geq 75\%$ /100% reduction in drop seizures (average per week) from baseline compared to the first 4 weeks/last 4 weeks of the maintenance period
- percent reduction in the number of total (drop and non-drop) seizures combined (average per week) from baseline compared to the maintenance period
- percent reduction in the number of non-drop seizures (average per week) from baseline compared to the maintenance period
- tolerance, as defined by the following:
 - a subject was classified as a treatment responder if he/she achieved at least a 50% reduction in their drop seizure rate within the first 4 weeks of the maintenance period compared to the 4 weeks of the baseline period. Using this definition of a treatment responder, the number and percentage of initial treatment responders who returned to their baseline drop seizure rate during the last 4 weeks of the maintenance period or discontinued the study for lack of efficacy were investigated.
 - a subject was classified as a treatment responder if he/she achieved at least a 50% reduction in their drop seizure rate within the first 8 weeks of the maintenance period when compared to the 4 weeks of the baseline period. Using this definition of a treatment responder, the number and percentage of initial treatment responders who returned to their baseline drop seizure rate during the last 4 weeks of the maintenance period or discontinued the study for lack of efficacy were investigated.
- physician global evaluation
- parent/caregiver global evaluation
- use of rescue medications

Reviewer's Note:

The primary efficacy variable was the percent reduction in drop seizures because drop seizures are the most injurious seizure type to the LGS patient. The sudden drops often result in head trauma and dental trauma; many patients must constantly wear helmets with face guards in an attempt to prevent injury. However, it might be possible that a drug might reduce the number of drug attacks but increase the number or severity of non-drop seizures also associated

with LGS, which would be a significant adverse effect. For this reason, the frequency of non-drop attacks is an important secondary outcome measure. Finally, as mentioned previously, the possibility of patients' developing tolerance to clobazam was a major concern. Patients have developed tolerance to other benzodiazepines which has limited their usefulness for chronic therapy of epilepsy. Therefore, tolerance was another important secondary outcome.

Analysis of Primary Efficacy Variable:

The efficacy analyses were performed on the modified intent-to-treat (MITT) population using all available data. The MITT population included all randomized subjects who received at least 1 dose of study drug, had baseline data, and had at least 1 daily seizure measurement in the maintenance period.

The primary efficacy endpoint was evaluated by the analysis of covariance (ANCOVA). The analysis was performed on a model with percent reduction in drop seizures as the dependent variable and treatment, pooled center, and baseline drop seizure rate as the independent variables. Ninety-five percent confidence intervals (CIs) were provided for the mean difference between each clobazam treatment group and placebo.

Superiority of clobazam to placebo ($p \leq 0.01$) was to be considered robust statistical evidence in a single multicenter study, consistent with FDA guidance. Statistical comparisons used a step-down procedure starting with the high-dose group versus placebo as the primary comparison. If not significant, all 3 clobazam dose groups were to be declared not statistically significantly different from placebo. If the high-dose group to placebo comparison was significant, then the procedure was to be repeated comparing the medium-dose group with placebo; if the medium dose versus placebo was not significant, then both the medium- and low-dose groups were to be declared not statistically significantly primary different from placebo. If the first 2 pairwise comparisons were significant (high dose versus placebo and medium dose versus placebo), then the procedure was to be repeated comparing the low-dose group with placebo.

The cumulative distribution of percent reduction in average weekly rate of drop seizures (ie, continuous responder curve) was summarized graphically. Analyses added after breaking the blind included a test for linear dose response, a 2-sided, pairwise comparison of each clobazam dose group versus placebo performed using the Wilcoxon rank-sum test (for median change from baseline), and a sensitivity analysis of all randomized subjects who received at least 1 dose of study drug, had baseline data, and had at least 1 daily measurement of drop seizures during the titration or maintenance period. This latter analysis was performed for the intent-to-treat (ITT) population, defined as all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the titration or maintenance period. All other sensitivity analyses were prespecified in the Statistical Analysis Plan

(SAP) for Study OV-1012. Finally, using efficacy data from Study OV-1012 only, a pharmacokinetic model was developed to determine the exposure-response relationship for clobazam and/or N-desmethyclobazam (N-CLB) and the primary endpoint of fractional reduction in number of drop seizures (average per week) from the 4-week baseline period compared to the 12-week maintenance period.

Analysis of Secondary and Additional Efficacy Variables

The following secondary and additional efficacy analyses were performed:

- percent of subjects considered treatment responders analyzed with logistic regression, with treatment, pooled center, and baseline seizure rate as factors
 - total (non-drop and drop) seizures and non-drop seizures, classified by seizure type per the International League Against Epilepsy (ILAE) summarized and analyzed using the same method as drop seizures
 - the physician global evaluation and parent/caregiver global evaluation analyzed by the Cochran-Mantel-Haenszel test, including treatment and pooled center effects
 - percent of subjects using rescue medications analyzed using a logistic regression model with treatment, baseline drop seizure rate, and pooled center as covariates
- Centers with fewer than 16 subjects randomized were pooled geographically combining the smallest center with the next smallest center of a particular region until at least 16 subjects were in each pooled center.

After breaking the blind, analysis of the rank-transformed percent reduction in average weekly rate of total (drop and non-drop) seizures and non-drop seizures was added. In addition, analyses based on an asymptotic Wald test of equality on the numbers of subjects whose physician and parent/caregiver evaluations were at least minimally improved and at least much improved were added after breaking the blind.

Results of Analyses

Baseline Characteristics and Disposition

A total of 238 subjects were randomized in the study: 59 subjects to the placebo group, 58 subjects to the low-dose (target dose of clobazam 0.25 mg/kg/day) group, 62 subjects to the medium-dose (target dose of clobazam 0.5 mg/kg/day) group, and 59 subjects to the high-dose (target dose of clobazam 1.0 mg/kg/day) group (Table 6). The majority of subjects were male (60.5%) and White/Caucasian (61.8%); mean age was 12.4 years.

Overall, 74.4% of subjects completed the study. The most common reasons for discontinuation were lack of efficacy in the placebo group and adverse event in the clobazam groups. The percentage of subjects prematurely discontinuing due to adverse events increased with clobazam dose (3.4% placebo, 6.9% low dose, 12.9% medium dose, and 20.3% high dose).

A total of 217 and 236 subjects are included in the MITT and ITT analyses, respectively.

Table 6 Patient Disposition for Study OV-1012

Study OV-1012 Status	Placebo	Dose Level			Total
		Low (0.25 mg/kg)	Medium (0.5 mg/kg)	High (1.0 mg/kg)	
Randomized, N	59	58	62	59	238
Completed, n (%)	41 (69.5)	50 (86.2)	45 (72.6)	41 (69.5)	177 (74.4)
Discontinued, n (%)	18 (30.5)	8 (13.8)	17 (27.4)	18 (30.5)	61 (25.6)
Discontinued due to AE, n (%)	2 (3.4)	4 (6.9)	8 (12.9)	12 (20.3)	26 (10.9)
Discontinued due to Lack of efficacy	10 (16.9)	1 (1.7)	4 (6.5)	0	15 (6.3)

Key Results

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF DROP SEIZURES

Compared with the placebo group, the medium-dose and high-dose clobazam groups met the criterion for robust statistical significance ($p \leq 0.01$) for mean percent reduction in average weekly rate of drop seizures from baseline to the maintenance period (Table 7).

In addition, the low-dose group was statistically significantly superior ($p \leq 0.05$) to the placebo group for this endpoint. An additional analysis demonstrated a statistically significant linear trend ($p < 0.0001$) of increasing efficacy with increasing dose. Statistical significance versus placebo was demonstrated using an ANCOVA model comparing mean percent reduction from baseline. Statistical significance versus placebo was also demonstrated using the Wilcoxon rank-sum test comparing median percent reduction from baseline, an analysis added after breaking the blind because of the highly non-normal distribution of the data.

A population pharmacokinetic exposure-response model found that clobazam administration in the presence of other AEDs was associated with a dose-related reduction in drop seizure frequency compared with baseline. The fraction of baseline daily average drop seizure frequency was correlated with the steady-state average concentrations (C_{avg}) for clobazam and N-CLB. The change in drop seizure frequency occurs more rapidly with increasing C_{avg} of clobazam than for N-CLB.

Table 7 Percent Reduction in Average Weekly Rate of Drop Seizures in Study OV-1012 - MITT Population

Parameter	Dose Level ¹			
	Placebo N = 57	Low N = 53	Medium N = 58	High N = 49
Baseline mean seizure rate	97.8	99.6	60.5	105.2
Baseline median seizure rate (range)	35.5 (2, 920)	29.2 (2, 1077)	22.5 (2, 798)	46.4 (2, 856)
Maintenance mean seizure rate	71.4	70.2	23.6	30.2
Maintenance median seizure rate (range)	26.0 (0, 676)	16.3 (0, 927)	6.9 (0, 173)	5.1 (0, 276)
LS mean percent reduction in seizure rate	12.1	41.2	49.4	68.3
Median percent reduction in seizure rate (range)	23.2 (-374, 100)	46.7 (-119, 100)	57.9 (-262, 100)	86.5 (-39, 100)
LS mean difference from placebo (95% CI)		29.1 (6.45, 51.73)	37.3 (14.38, 60.13)	56.1 (33.38, 78.88)
p-value: comparison to placebo ²		0.0120	0.0015	< 0.0001
p-value: comparison to placebo ³		0.0170	0.0002	< 0.0001
p-value: linear trend ⁴		< 0.0001		

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CI = confidence interval; LS = least squares

Note: The MITT population is all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the maintenance period; for subjects missing some of the daily measurements, the available data were used.

¹ Low-, Medium-, and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg), 0.5 mg/kg of clobazam (up to a maximum daily dose of 20 mg), and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, and baseline seizure rate included as effects in the model.

³ 2-sided pairwise comparison comparing each active dose level to placebo using the Wilcoxon rank-sum test. This analysis was added after breaking the blind.

⁴ Analysis was added after breaking the blind.

Source: OV-1012 Table 14.2.1.1

Sensitivity Analyses

The following sensitivity analyses for the percent reduction in the average weekly rate of drop seizures from baseline to the maintenance period were conducted to examine the effects of demographic factors, imputation of missing data, data transformation, and blind breaking.

A: Accounting for country, with an ANCOVA model including treatment, country, and baseline seizure rate included as effects

B: Not accounting for centers or country, with an ANCOVA model including treatment and baseline seizure rate included as effects

C: Using seizure count = 20 if "10-20" box was checked and 30 if "> 20" box was checked with an ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

D: Using seizure count = 20 if "10-20" box was checked and 50 if "> 20" box was checked with an ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

E: Analyzing logarithm of (baseline seizure rate + 1) minus logarithm of (maintenance rate + 1) with seizure count = 10 if "10-20" box was checked and 20 if "> 20" box was checked with an ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

F: Analyzing logarithm of (baseline seizure rate + 1) minus logarithm of (maintenance rate + 1) with seizure count = 20 if "10-20" box was checked and 30 if "> 20" box was checked with an ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

G: Analyzing logarithm of (baseline seizure rate + 1) minus logarithm of (maintenance rate + 1) with seizure count = 20 if "10-20" box was checked and 50 if "> 20" box was checked with an

ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

H: Adjusting for weight, age, and gender with an ANCOVA model including treatment, pooled center, weight category at randomization, age, gender, and baseline seizure rate as effects

I: Imputing baseline seizure rate for remainder of maintenance period if subject discontinued due to adverse event, with an ANCOVA model including treatment, pooled center, and baseline seizure rate included as effects

J: Excluding observations obtained after blind break, with an ANCOVA model including treatment, pooled center, and baseline seizure rate included as effects (The sponsor instructed Site 700 to record the blind as broken for all 7 subjects [OV-1012 Listing 16.2.5.2]) when documentation with study drug identification was inadvertently sent to the site by the warehouse. This sensitivity analysis excludes these 7 subjects.)

K: Using rank of percent reduction as the response variable with an ANCOVA model including treatment, pooled center, and baseline seizure rate as effects

L: Using primary variable and ANCOVA with all randomized subjects who received at least 1 dose of study drug, had baseline data, and had at least 1 daily measurement of drop seizures during the titration or maintenance period (analysis added after breaking the blind).

The medium-dose and high-dose groups of clobazam were statistically significantly superior to the placebo group for all sensitivity analyses, and met the criterion for robust statistical significance ($p \leq 0.01$) (Table 8). The low-dose group of clobazam was statistically significantly superior ($p \leq 0.05$) to the placebo group for all sensitivity analyses except those on logarithm-transformed reductions in drop seizures.

Table 8 Sensitivity Analysis of Reduction in Average Weekly Rate of Drop Seizures in OV-1012 (Baseline to Maintenance Period) - MITT and ITT Populations

Sensitivity Analysis	Dose Level ¹			
	Placebo N = 57	Low N = 53	Medium N = 58	High N = 49
A: LS mean percent reduction in seizure rate p-value: comparison to placebo ³	10.6	39.1 0.0119	45.7 0.0016	66.9 < 0.0001
B: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁴	12.4	41.5 0.0088	48.1 0.0011	69.3 < 0.0001
C: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁵	11.1	39.6 0.0219	47.6 0.0039	67.8 < 0.0001
D: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁵	10.6	39.9 0.0202	47.3 0.0042	67.6 < 0.0001
E: LS mean change in log seizure rate p-value: comparison to placebo ⁵	0.43	0.81 0.0741	1.09 0.0021	1.77 < 0.0001
F: LS mean change in log seizure rate p-value: comparison to placebo ⁵	0.44	0.80 0.1006	1.11 0.0030	1.83 < 0.0001
G: LS mean change in log seizure rate p-value: comparison to placebo ⁵	0.44	0.81 0.1106	1.13 0.0032	1.85 < 0.0001
H: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁶	13.4	41.6 0.0159	50.6 0.0017	69.0 < 0.0001
I: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁵	11.0	40.1 0.0114	45.0 0.0036	62.5 < 0.0001
J: LS mean percent reduction in seizure rate p-value: comparison to placebo ⁵	10.5	40.9 0.0100	49.4 0.0014	68.8 < 0.0001
K: p-value: comparison to placebo ⁵		0.0274	0.0004	< 0.0001
L: ITT sample sizes	N = 58	N = 58	N = 61	N = 59
LS mean percent reduction in seizure rate	8.6	30.9	37.9	44.0
p-value: comparison to placebo ⁵		0.0029	0.0001	< 0.0001

LS = least squares

Note: The MITT population (analyses A through K) is all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the maintenance period. The ITT population (analysis L) is all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the titration or maintenance period. For subjects missing some of the daily measurements, the available data were used.

¹ Low-, Medium-, and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg), 0.5 mg/kg of clobazam (up to a maximum daily dose of 20 mg), and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² Sample sizes represent the MITT population for analyses A through K. Sample sizes for the ITT population are shown for analysis L.

³ 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, country, and baseline seizure rate included as effects in the model.

⁴ 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment and baseline seizure rate included as effects in the model.

⁵ 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, and baseline seizure rate included as effects in the model.

⁶ 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, weight category at randomization, age, gender, and baseline seizure rate included as effects in the model.

Source: OV-1012 Tables 14.2.1.3, 14.2.1.4, 14.2.1.5, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9, and 14.2.1.13

PERCENT REDUCTION IN TOTAL (DROP AND NON-DROP) SEIZURES FROM BASELINE TO MAINTENANCE PERIOD

All dose groups of clobazam were statistically significantly superior to the placebo group for percent reduction in average weekly rate of total (drop and non-drop) seizures from baseline to the maintenance period (Table 9). The p-values for comparison of the medium-dose and high-dose groups with placebo were < 0.01. Statistical significance versus placebo was demonstrated using an ANCOVA model comparing mean percent reduction from baseline.

Statistical significance versus placebo was also demonstrated using the Wilcoxon rank-sum test comparing median percent reduction from baseline, an analysis added after breaking the blind because of the highly non-normal distribution of the data.

Table 9 Percent Reduction in Average Weekly Rate of Total (Drop and Non-drop) Seizures in OV-1012 (Baseline to Maintenance Period) – MITT Population

Parameter	Dose Level ¹			
	Placebo N = 57	Low N = 53	Medium N = 58	High N = 49
Baseline mean seizure rate	117.1	131.1	111.5	128.7
Baseline median seizure rate (range)	46.8 (4, 920)	45.5 (4, 1125)	36.6 (3, 1465)	80.6 (2, 864)
Maintenance mean seizure rate	91.9	90.3	38.1	41.9
Maintenance median seizure rate (range)	34.9 (0, 694)	32.0 (0, 977)	14.1 (0, 192)	10.0 (0, 285)
LS mean percent reduction in seizure rate	9.3	34.8	45.3	65.3
Median percent reduction in seizure rate (range)	11.3 (-189, 100)	43.1 (-155, 100)	62.1 (-523, 100)	82.8 (-49, 100)
LS mean difference from placebo (95% CI)		25.5 (1.00, 49.96)	35.9 (11.35, 60.53)	56.0 (31.40, 80.57)
p-value: comparison to placebo ²		0.0414	0.0044	< 0.0001
p-value: comparison to placebo ³		0.0040	< 0.0001	< 0.0001

CI = confidence interval; LS = least squares

Note: The MITT population is all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the maintenance period; for subjects missing some of the daily measurements, the available data were used.

¹ Low-, Medium-, and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg), 0.5 mg/kg of clobazam (up to a maximum daily dose of 20 mg), and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, and baseline seizure rate included as effects in the model.

³ 2-sided pairwise comparison comparing each active dose level to placebo using the Wilcoxon rank-sum test. This analysis was added after breaking the blind.

Source: [OV-1012 Table 14.2.2.4](#)

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NDA 202067
Onfi (Clobazam)

Results were similar when the rank-transformed percent reduction in average weekly rate of total (drop and non-drop) seizures was analyzed with the same ANCOVA model, an analysis added after breaking the blind. P-values for the comparison to placebo were 0.0179 for the low-dose group and < 0.0001 for the medium-dose and high-dose groups.

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF NON-DROP SEIZURES FROM BASELINE TO MAINTENANCE PERIOD

All dose groups of clobazam were numerically superior to the placebo group for percent reduction in average weekly rate of non-drop seizures from baseline to the maintenance period, but statistically significant mean differences from the placebo group were not observed for prespecified ANCOVA analyses (Table 10). However, the high-dose group was statistically significantly superior to placebo using the Wilcoxon rank-sum test, an analysis added after breaking the blind because of the highly non-normal distribution of the data.

Mean differences from the placebo group increased with increasing dose of clobazam (mean differences of 23.0%, 73.0%, and 116.3% for the low-dose, medium-dose, and high-dose groups, respectively).

Table 10 Percent Reduction in Average Weekly Rate of Non-drop Seizures in Study OV-1012 (Baseline to Maintenance Period) – MITT Population

Parameter	Dose Level ¹			
	Placebo N = 57	Low N = 53	Medium N = 58	High N = 49
Number of subjects with non-drop seizures	41	36	43	26
Baseline mean seizure rate	23.5	41.5	64.9	42.5
Baseline median seizure rate (range)	10.0 (0, 254)	18.0 (0, 228)	14.6 (0, 1410)	32.0 (0, 168)
Maintenance mean seizure rate	25.4	28.8	18.7	21.6
Maintenance median seizure rate (range)	4.4 (0, 263)	16.9 (0, 152)	5.1 (0, 146)	2.9 (0, 237)
LS mean percent reduction in seizure rate	-76.3	-53.3	-3.3	40.0
Median percent reduction in seizure rate (range)	34.4 (-1477, 97)	17.9 (-1627, 100)	49.4 (-1591, 100)	76.5 (-190, 100)
LS mean difference from placebo (95% CI)		23.0 (-104.1, 150.14)	73.0 (-52.11, 198.09)	116.3 (-19.42, 252.07)
p-value: comparison to placebo ²		0.7210	0.2505	0.0924
p-value: comparison to placebo ³		0.5710	0.1422	0.0056

CI = confidence interval; LS = least squares

Note: The MITT population is all randomized subjects who had baseline data, at least 1 dose of study drug, and at least 1 daily seizure measurement during the maintenance period; for subjects missing some of the daily measurements, the available data were used.

¹ Low-, Medium-, and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg), 0.5 mg/kg of clobazam (up to a maximum daily dose of 20 mg), and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² 2-sided pairwise comparison comparing each active dose level to placebo using an ANCOVA model with treatment, pooled center, and baseline seizure rate included as effects in the model.

³ 2-sided pairwise comparison comparing each active dose level to placebo using the Wilcoxon rank-sum test. This analysis was added after breaking the blind.

Source: [OV-1012 Table 14.2.2.5](#)

The high-dose group was statistically significantly different from the placebo group ($p = 0.0070$) when the rank-transformed percent reduction in average weekly rate of non-drop seizures was analyzed with the same ANCOVA model), an analysis added after breaking the blind. P-values for comparison to placebo for the low-dose and medium-dose groups were 0.4818 and 0.2224, respectively.

Conclusions for Study OV-1012

The medium-dose and high-dose levels of clobazam met the criterion for robust statistical significance ($p \leq 0.01$) versus placebo for reduction from baseline to maintenance in average weekly rate of drop seizures. In addition, the low-dose group was statistically significantly superior ($p \leq 0.05$) to the placebo group. An additional analysis demonstrated a statistically significant linear trend ($p < 0.0001$) of increasing efficacy with increasing dose.

Sensitivity analyses were conducted to examine the effects of demographic factors, imputation of missing data, and data transformation. The medium-dose and high-dose groups of clobazam were statistically significantly superior to the placebo group for all sensitivity analyses, and met the criterion for robust statistical significance ($p \leq 0.01$). The low-dose group of clobazam was statistically significantly superior ($p \leq 0.05$) to the placebo group for all sensitivity analyses except those on logarithm-transformed reductions in drop seizures.

Results for secondary and additional efficacy analyses were consistent with the primary efficacy analysis. Key results for these analyses included:

- Statistically significantly greater percent reductions in average weekly rate of drop seizures from baseline to the first 4 weeks of the maintenance period were observed in all dose groups of clobazam compared to placebo.
- The percent of subjects with $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, and 100% reduction from baseline to the maintenance period in the average weekly rate of drop seizures was higher in each of the clobazam groups compared to the placebo group. For the medium-dose and high-dose groups of clobazam, the difference from the placebo group was statistically significant for $\geq 25\%$, $\geq 50\%$, and $\geq 75\%$ reduction. For the low-dose group of clobazam, the difference from the placebo group was statistically significant for $\geq 75\%$ reduction. For the proportion of subjects with 100% reduction, the logistic regression model was unable to provide valid estimates.
- All clobazam dose groups showed statistical superiority (medium-/high-dose groups $p \leq 0.01$; low-dose group $p \leq 0.05$) to placebo in average weekly rate of total seizures (drop and non-drop), and p-values for comparison of medium- and high-dose groups with placebo were below 0.01.
- All dose groups of clobazam were numerically superior to the placebo group for percent reduction in average weekly rate of non-drop seizures from baseline to the maintenance period. Mean differences from the placebo group increased with increasing dose of clobazam.
- The percent of subjects who were assessed by the physician as at least much improved (i.e., much improved or very much improved) and at least minimally improved (i.e., minimally improved, much improved, or very much improved) from baseline at end of maintenance was statistically significantly higher in each of the clobazam groups compared to the placebo group.
- The percent of subjects who were assessed by the parent/caregiver as at least much improved from baseline at end of maintenance was statistically significantly higher in the medium-dose and high-dose groups compared to the placebo group. The percent of subjects who were at least minimally improved from baseline at end of maintenance was statistically significantly higher in each of the clobazam groups compared to the placebo group.

Reviewer Conclusion: Pivotal Study OV-1012 provides solid statistical and clinical evidence for the efficacy of clobazam in the adjunctive treatment of both

the drop and non-drop seizures associated with LGS. The incidence of tolerance was acceptably low during the 12 week maintenance period. It shows increasing efficacy with increasing dose. The adverse effects also increase with dose but remain in the acceptable range at the doses used. Therefore, the proposed indication for adjunctive treatment of all seizure types associated with LGS and the proposed dosage are appropriate.

As discussed immediately below in this review, the efficacy of clobazam is further supported by the earlier, supportive study OV-1002 and by the follow-on study OV-1004.

As an orphan product, the evidence from one robust pivotal efficacy study in addition to good supportive evidence is sufficient for approval with regard to efficacy. Clinical review approval also requires demonstration of safety, the subject of a separate review by Dr. Gerard Boehm.

Supportive Study for Efficacy OV-1002

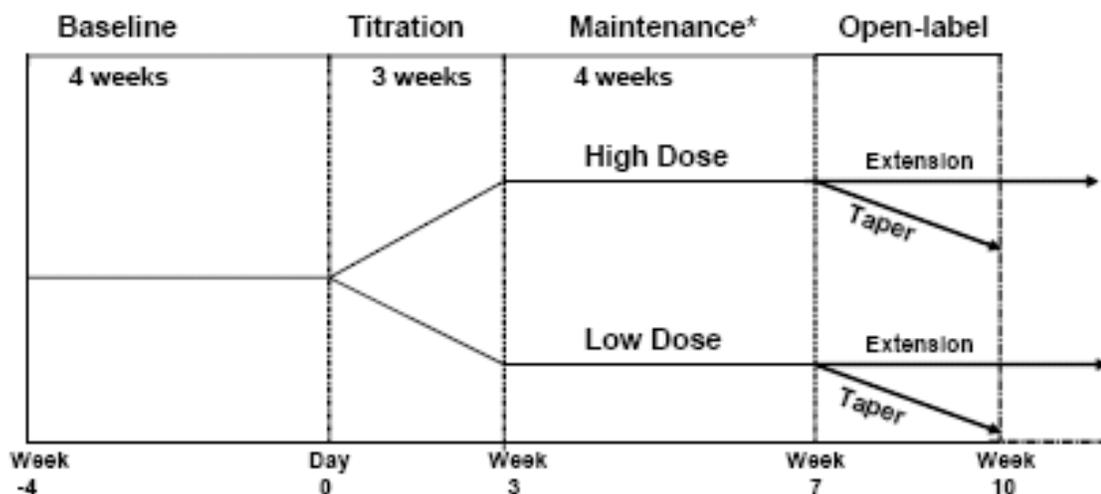
The Phase 2 supportive dose-ranging study was entitled “Multicenter, randomized, double-blind, dose-ranging study designed to assess the safety and efficacy of clobazam as adjunctive therapy in subjects 2-30 years of age with Lennox-Gastaut Syndrome”.

Design:

Study OV-1002 was a Phase 2, multicenter, randomized, double-blind, dose-ranging, parallel-group study designed to assess the efficacy and safety of clobazam as adjunctive therapy to a stable regimen of AEDs in subjects 2-30 years of age with LGS. The study comprised a 4-week baseline period, a 3-week titration period, a 4-week maintenance period, and a taper period of up to 3 weeks, with a final visit 1 week after last dose for subjects not continuing in the open-label extension study (OV-1004). The study schematic is presented in Figure 4 from the Sponsor’s ISE.

Figure 2 Schematic for Study OV-1002 (Sponsor's ISE Figure 4)

Figure 4. Schematic for Study OV-1002



* Subjects not directly continuing into the open-label extension study tapered off study drug (up to a 3-week taper period), with the final visit 1 week post last dose.

Reviewer Note:

In comparison to the later pivotal Phase 3 Study OV 1012, Study OV-1002 had no placebo arm. However, as discussed below, the comparison of the high dose to low dose provides further evidence of efficacy. OV-1002 had only the high and low dose arms (not the middle dose arm) used in OV-1012. Furthermore, the 4 weeks maintenance period of OV-1002 was too short to address the issue of developing tolerance to the efficacious effect of clobazam; this was addressed by the longer (12 weeks) maintenance period of Study OV 1012.

Subjects were stratified into 1 of 6 prespecified weight categories (12.5-17.5 kg, 17.6-22.5 kg, 22.6-27.5 kg, 27.6-32.5 kg, 32.6-37.5 kg, > 37.6 kg) on Day -28. On Day -1, qualifying subjects were randomly assigned to a low dose (target dose of 0.25 mg/kg [up to a maximum daily dose of 10 mg]) or high dose (target dose of 1.0 mg/kg [up to a maximum daily dose of 40 mg]) of clobazam. During the 3-week titration period (office visits at Weeks 1, 2, and 3), subjects began taking either 5 mg or 10 mg clobazam daily in divided doses, increasing the dose every 7 days until the target dose was attained. The target dose was then administered for 4 weeks (maintenance period). Study medication was administered BID with doses in the morning and at bedtime; when the daily dose could not be equally divided between the morning and evening dose, the higher dose was to be given in the evening. After the maintenance period, an unblinded physician was able to appropriately adjust the subject's dose during the Study OV-1002 taper period (up to 3 weeks) or upon transition to the open-label extension study (OV-1004). In addition, the unblinded physician may have continued to treat the subject in

the open-label study. The Investigator remained blinded to the dose assignment until being unblinded by the sponsor or until unblinding was required for the subject's safety.

At any time during the study, beginning with the second week of the titration period, if a subject developed any sign or symptom that represented difficulty tolerating study drug, the Investigator could have reduced the daily dosage by one 5 mg tablet. The minimum clobazam dose was 5 mg/day. In order to remain blinded, for subjects only on 5 mg per day, the reduction in medication was a placebo tablet, not clobazam. Subjects who could not tolerate the target dose or the decreased dose were discontinued from the study but may have been eligible to enter into the open-label extension study (OV-1004).

Subjects were allowed rescue therapy of 1 rescue per day with no more than a total of 4 days in 4 weeks (average of 1 rescue dose per week). Rescue treatment options could have included, but were not limited to, diazepam and lorazepam. Clobazam was not to be used as a rescue medication.

Seizures were to be recorded on a daily basis in seizure diaries by the parent/caregiver, with the assistance of the subject, if able. Seizure rates were calculated and summarized as weekly averages. Baseline seizure rates were calculated from the 4-week baseline period that preceded randomization. The weekly number of drop seizures during baseline was the number of drop seizures reported during baseline divided by the number of days recorded during baseline multiplied by 7. Similarly, the weekly number of drop seizures during maintenance was the number of drop seizures reported during maintenance divided by the number of days during maintenance multiplied by 7.

Inclusion/Exclusion:

In order to qualify for the study, subjects had to have a diagnosis of LGS, including written documentation of having met EEG diagnostic criteria at some point in their history, and evidenced by more than one type of generalized seizure, including drop seizures (atonic, tonic, or myoclonic) for at least 6 months. Subjects must also have experienced at least 2 drop seizures per week during the baseline period and had been taking a stable regimen of 1 to 3 AEDs, which could have included vagal nerve stimulator (VNS) and/or ketogenic diet, for at least 4 weeks prior to screening. The only prohibited AEDs were benzodiazepines, except as rescue medications, per the inclusion criteria.

Outcome Measures:

The primary efficacy variable was the percent reduction in drop seizures (average per week) from the 4-week baseline period compared to the 4-week maintenance period. A positive value of the percent reduction in drop seizures indicated a reduction in the number of drop seizures.

The secondary and additional efficacy variables include:

- percent reduction in total (drop and non-drop) seizure types from the baseline period compared to the 4-week maintenance period (analysis of performed for the sponsor's ISE only)
- percent of subjects considered treatment responders, defined as those with a $\geq 25\%$ / $\geq 50\%$ / $\geq 75\%$ / $\geq 100\%$ reduction in drop seizures from the baseline period compared to the 4-week maintenance period
- percent reduction in non-drop seizure types from the baseline period compared to the 4-week maintenance period
- physician global evaluation
- parent/caregiver global evaluation
- use of rescue medications

Reviewer's note:

As in Pivotal Study OV-1012, this Study OV-1002 focused on drop seizures for the primary outcome since these are the most injurious to the patients. However, both drop and non-drop seizures were again found to be responsive to clobazam as in Study OV-1012.

Analysis of Primary Efficacy Variable:

The primary population for efficacy analyses was the MITT population. The MITT population consisted of all randomized subjects who received study drug, had both a baseline and post-baseline measurement, and had at least 1 measurement during the maintenance period.

The 1-sided Wilcoxon signed rank test was used to assess the difference from baseline for each dose group. As a supportive efficacy analysis, the 1-sided Wilcoxon rank-sum test was used to compare the high-dose to the low-dose group. The average percent reduction in seizures per week for subjects who did not complete the 4-week maintenance period was calculated based on the time from the beginning of the maintenance period to the date of withdrawal.

Analysis of Secondary and Additional Efficacy Variables:

The following secondary and additional efficacy analyses were performed:

- A 1-sided Fisher's exact test was used to compare the proportion of responders in the high-dose group to the proportion in the low-dose group. The average drop in seizures per week for subjects who did not complete the 4-week maintenance period was calculated based on the date of withdrawal.
- Responses to the physician and parent/caregiver evaluations were recorded using 7-point Likert scales. These were treated as continuous variables and analyzed with a 1-sided t-test.

- The percent reduction in non-drop seizures, classified by seizure type per the ILAE was summarized and analyzed using the same method as drop seizures
- The use of rescue medication was compared between the groups using the Wilcoxon rank-sum test.

In addition, an analysis of total (drop and non-drop) seizures was performed.

Baseline Characteristics and Disposition

A total of 68 subjects were randomized in the study: 32 to the low-dose (target dose of clobazam 0.25 mg/kg/day) group and 36 to the high-dose (target dose of clobazam 1.0 mg/kg/day) group. The majority of the subjects were White/Caucasian (86.8%). Age ranged from 2-26 years (mean of 9 years). There were more males (61.8%) than females (38.2%).

Table 11 Patient Disposition for Study OV-1002

Study OV-1002	Clobazam	Clobazam	
Status	Low Dose (0.25 mg/kg/day)	High Dose (1.0 mg/kg/day)	Total
Randomized, N	32	36	68
Completed, n (%)	28 (87.5)	30 (83.3)	58 (85.3)
Discontinued, n (%)	4 (12.5)	6 (16.7)	10 (14.7)
Discontinued due to AE, n (%)	3 (9.4)	6 (16.6)	9 (13.2)

Overall, 85% of the subjects completed the study and 15% discontinued prematurely (Table 11). More subjects withdrew due to adverse events in the high-dose group (17%, 6 of 36 subjects) than in the low-dose group (9%, 3 of 32 subjects). A total of 61 subjects are included in the MITT analyses (Table 12).

Key results OV-1002

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF DROP SEIZURES

Treatment with both low- and high-dose clobazam resulted in statistically significant percent reductions in the average weekly rate of drop seizures (Table 12). The median reduction in average weekly rate of drop seizures was 41% ($p = 0.0162$) in the low-dose group and 93% ($p < 0.0001$) in the high-dose group. The difference between the treatment group medians was 44.7% and was statistically significantly in favor of the high-dose group ($p < 0.0001$, 95% CI 21.7% to 66.7%).

Reviewer Note:

Although there was no placebo arm, Study OV-1002 demonstrated efficacy by showing superiority of the high dose over the low dose. The Sponsor could well argue that they are presenting two pivotal efficacy studies rather than a pivotal study (OV-1012) and a supportive study (OV-1002). However, as discussed above, Study OV-1012 was a better pivotal study because it had a larger enrollment, a placebo control arm, three dosage levels showing dose-responsiveness, and a long maintenance period to rule out development of tolerance to the efficacious effect.

Table 12 Percent Reduction in Average Weekly Rate of Drop Seizures in Study OV-1002 (Baseline to Maintenance Period) – MITT Population

Parameter	Dose Level ¹	
	Low N = 29	High N = 32
Baseline mean seizure rate	141.0	206.5
Baseline median seizure rate (range)	66 (5, 661)	97 (8, 924)
Maintenance mean seizure rate	91.3	31.9
Maintenance median seizure rate (range)	27 (0, 470)	4 (0, 198)
Mean percent reduction in seizure rate	12.0	85.3
Median percent reduction in seizure rate (range)	41 (-531, 100)	93 (48, 100)
p-value for within-group percent reduction ²	0.0162	< 0.0001
Treatment difference (95% CI) ³	44.7 (21.7, 66.7)	
p-value for treatment difference ⁴	< 0.0001	

CI = confidence interval

¹ Low- and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg) and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² p-values for within-group percent reduction from 1-sided Wilcoxon signed rank test

³ Hodges-Lehman estimate and 95% CI for the difference in median percent reduction (high versus low dose)

⁴ p-values for treatment difference (high versus low dose) from 1-sided Wilcoxon rank-sum test

Source: [OV-1002 Table 7](#)

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF TOTAL (DROP AND NON-DROP) SEIZURES

Treatment with both low- and high-dose clobazam resulted in statistically significant percent reductions in the average weekly rate of total (drop and non-drop) seizures (Table 13). The median reduction in average weekly rate of total seizures was 27% (p = 0.0388) in the low-dose group and 86% (p < 0.0001) in the high-dose group. The difference between the treatment group medians was 53.5% and was statistically significantly in favor of the high-dose group (p < 0.0001, 95% CI 27.0% to 74.2%).

Table 13 Percent Reduction in Average Weekly Rate of Total (Drop and Non-drop) Seizures in Study OV-1002 (Baseline to Maintenance Period) – MITT Population

Parameter	Dose Level ¹	
	Low N = 29	High N = 32
Baseline mean seizure rate	153.3	216.6
Baseline median seizure rate (range)	88.1 (9, 665)	105 (9, 927)
Maintenance mean seizure rate	112.3	36.9
Maintenance median seizure rate (range)	48 (0, 508)	13 (0, 198)
Mean percent reduction in seizure rate	19.1	81.5
Median percent reduction in seizure rate (range)	27 (-129, 100)	86 (29, 100)
p-value for within-group percent reduction ²	0.0388	< 0.0001
Treatment difference (95% CI) ³	53.5 (27.0, 74.2)	
p-value for treatment difference ⁴	< 0.0001	

CI = confidence interval

¹ Low- and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg) and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

² p-values for within-group percent reduction from 1-sided Wilcoxon signed rank test

³ Hodges-Lehman estimate and 95% CI for the difference in median percent reduction (high versus low dose)

⁴ p-values for treatment difference (high versus low dose) from 1-sided Wilcoxon rank-sum test

Source: ISE Table 17

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF NON-DROP SEIZURES FROM BASELINE TO MAINTENANCE PERIOD

Subjects receiving the higher dose of clobazam had a statistically significant percent reduction in average weekly rate of non-drop seizures from baseline to maintenance (Table 14). The median reduction in average weekly rate of non-drop seizures was 86% (p < 0.0001) in the high-dose group and 16% (p = 0.1466) in the low-dose group. The difference between the treatment groups was statistically significant in favor of the high-dose group (p = 0.0222).

Table 14 Percent Reduction in Average Weekly Rate of Non-drop Seizures in Study OV-1002 (Baseline to Maintenance Period) – MITT Population

Parameter	Dose Level ¹	
	Low N = 29	High N = 32
Baseline number of subjects with non-drop seizures	22	24
Baseline mean seizure rate	15.1	9.7
Baseline median seizure rate (range)	5 (0, 76)	6 (0, 39)
Maintenance number of subjects with non-drop seizures	22	23
Maintenance mean seizure rate	19.1	5.9
Maintenance median seizure rate (range)	3 (0, 117)	1 (0, 47)
Percent reduction N	19	22
Mean percent reduction in seizure rate	8.5	59.2
Median percent reduction in seizure rate (range)	16 (-204, 100)	86 (-86, 100)
p-value for within-group percent reduction ²	0.1466	< 0.0001
Treatment difference (95% CI) ³	29.7 (0.0, 89.5)	
p-value for treatment difference ⁴	0.0222	

CI = confidence interval

- ¹ Low- and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg) and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.
- ² p-values for within-group percent reduction from 1-sided Wilcoxon signed rank test
- ³ Hodges-Lehman estimate and 95% CI for the difference in median percent reduction (high versus low dose)
- ⁴ p-values for treatment difference (high versus low dose) from 1-sided Wilcoxon rank-sum test

Source: [OV-1002 Table 13.1](#)

Secondary endpoints OV-1002:

Results for secondary and additional efficacy analyses were consistent with the primary efficacy analysis. Key results for these analyses included:

- Statistically significant differences were observed between the high-dose and low-dose groups in the percent of subjects with $\geq 25\%$, with $\geq 50\%$, and with $\geq 75\%$ reduction in the weekly drop seizure rate. The percentage of subjects with 100% reduction in drop seizures was greater in the high-dose group (22%) than in the low-dose group (6%), but the difference was not statistically significant.
- Treatment with both low- and high-dose clobazam resulted in statistically significant percent reductions in the average weekly rate of total (drop and non-drop) seizures. The median reduction in average weekly rate of total seizures was 27% in the low-dose group and 86% in the high-dose group. The difference between the treatment group medians was 53.5% and was statistically significantly in favor of the high-dose group.
- Subjects receiving the higher dose of clobazam had a statistically significant percent reduction in average weekly rate of non-drop seizures from baseline to maintenance. The median reduction in average weekly rate of non-drop seizures was 86% in the high-

dose group and 16% in the low-dose group. The difference between the treatment groups was statistically significant in favor of the high-dose group.

- The percent of subjects who were assessed by the physician as at least much improved (ie, much improved or very much improved) and at least minimally improved (ie, minimally improved, much improved, or very much improved) from baseline at end of maintenance was statistically significantly higher in the high-dose group compared to the low-dose group.
- The percent of subjects who were assessed by the parent/caregiver as at least much improved (i.e., much improved or very much improved) and at least minimally improved (ie, minimally improved, much improved, or very much improved) from baseline at end of maintenance was statistically significantly higher in the high-dose group compared to the low-dose group.

Reviewer Conclusion:

This study OV-1002 supports the results of the pivotal study (OV-1012) and provides further evidence for the efficacy of clobazam in the adjunctive treatment of seizure types (both drop and non-drop seizures) associated with LGS. The maintenance period is too short to address the issue of tolerance (as addressed in pivotal Study OV-1012). Study OV-1002 does support the dosing proposed by the sponsor by showing superior efficacy of the high dose arm over the low dose arm.

Supportive Study OV-1004

Ongoing multicenter open-label uncontrolled extension study of subjects from OV-1002 and OV-1012 to assessing long-term safety and efficacy of clobazam as adjunctive therapy in subjects with Lennox-Gastaut Syndrome

Design:

Study OV-1004 is an ongoing, multicenter, open-label study designed to assess the long-term safety and effectiveness of clobazam as adjunctive therapy for the treatment of seizures in subjects with LGS. Qualifying subjects from Studies OV-1002 and OV-1012 were given the option of continuing in this open-label study whether or not they discontinued from the previous blinded study, except if they had a serious or severe adverse event in the previous blinded study which, in the opinion of the Investigator, was probably or definitely related to clobazam and precluded safe use of clobazam. If > 14 days had elapsed since the subject received his/her last dose of study drug in the previous LGS study, the subject was not eligible for participation in the open-label study. For US subjects, the open-label study consists of a treatment period that lasts until clobazam is commercially available or until research on clobazam is discontinued in this indication. For ex-US subjects, the open-label study consists of a treatment period of up to 24 months or until research on clobazam is discontinued. Continuation on clobazam after 24 months is decided on a country by country basis and is based on medical need,

availability and access to clobazam and other AEDs, and discussions with physicians in each country.

Study visits are scheduled on Day 1, Week 1 (only for subjects from Study OV-1012), Months 1, 2, 3, 6, 9, 12, and every 6 months thereafter. During the week preceding each study visit throughout the treatment period, the parent/caregiver, with the assistance of the subject if able, maintains a seizure diary in which they record daily counts of seizures, including drop seizures. This is in contrast to controlled Studies OV-1012 and OV-1002, for which seizure diary data were collected during each week of study participation.

Analysis of Data:

The cutoff date for inclusion of data is 01 July 2010.

For subjects who received placebo in Study OV-1012, baseline corresponded to the last 7 non-missing diary days from Study OV-1012. For all other subjects, baseline was calculated from the last 7 non-missing diary days from the baseline period of the preceding study (OV-1002 or OV-1012).

The efficacy analysis set included all subjects who received at least 1 dose of clobazam in Study OV-1004 and had at least 1 efficacy measurement during the study. For subjects who received clobazam in the previous study, data from the previous study were combined for analysis with data collected during Study OV-1004. All summaries were descriptive and no formal hypothesis testing was performed.

Efficacy was summarized for the efficacy analysis set with descriptive statistics for the following groups of subjects unless specified otherwise.

- 6-month subset (subjects received their first dose of clobazam \geq 6 months but $<$ 12 months before data cutoff for this submission)
- 12-month subset (subjects received their first dose of clobazam \geq 12 months but $<$ 24 months before data cutoff)
- 24-month subset (subjects received their first dose of clobazam \geq 24 months before data cutoff)
- Total: all subjects in the efficacy analysis set (ie, total cohort of all subjects or Total subjects)

These subsets represent mutually exclusive cohorts of subjects based on the timing of the first dose of clobazam, whether in the previous blinded study or Study OV-1004, compared with the data cutoff. These subsets do not necessarily represent length of exposure to clobazam. Therefore, subjects may not have completed the full potential duration of their cohort. For example, a subject in the 24-month subset may have only completed 2 months of clobazam treatment. Summarizing efficacy for each of these

subsets partially controls for any difference in efficacy due to rolling accrual of subjects from the previous blinded studies OV 1002 and OV-1012.

Analyses of Drop Seizures

Reduction in drop seizures was calculated as the weekly number of drop seizures during baseline minus the number of seizures in the week preceding each study visit. Percent reduction in drop seizures was summarized descriptively at the evaluation times specified in Table 15 from the sponsor's ISE Table 24.

Table 15 Evaluation Windows for Assigning Post-baseline Efficacy Evaluations in Study OV-1004 (Sponsor's ISE Table 24)

Table 24. Evaluation Windows for Assigning Post-baseline Efficacy Evaluations in Study OV-1004

Assigned	Evaluation Day of Window
Month 3	90 (\pm 45 days)
Month 6	180 (\pm 45 days)
Month 9	270 (\pm 45 days)
Month 12	360 (-45 days to + 90 days)
Month 18	540 (\pm 90 days)
Month 24	720 (\pm 90 days)

Note: Day 1 was day on which the first dose of clobazam was received, whether in the previous blinded study or Study OV-1004.

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At each evaluation, the number and percent of subjects who achieved the following reductions from baseline in drop seizures were summarized.

- Any reduction from baseline
- \geq 25% reduction from baseline
- \geq 50% reduction from baseline
- \geq 75% reduction from baseline
- 100% reduction from baseline

Analyses of Other Key Efficacy Variables

An analysis of total (drop and non-drop) seizures is added after finalization of the Study OV-1004 SAP and is included in the Sponsor's ISE.

Percent reductions from baseline in non-drop seizures by type were summarized descriptively at the evaluation times specified in Table 15 and only for seizures types reported by at least 25 subjects at baseline. Categorical variables (physician global evaluation and parent/caregiver global evaluation) were summarized by the number and

percent of subjects in various improvement categories (eg, much improved, very much improved, minimally improved).

A cross-tabulation of subjects by the number of concomitant AEDs at baseline and final evaluation was summarized. The number of concomitant AEDs received by each subject at baseline and final evaluation were categorized as 1, 2, 3, and > 3.

Baseline Characteristics and Disposition

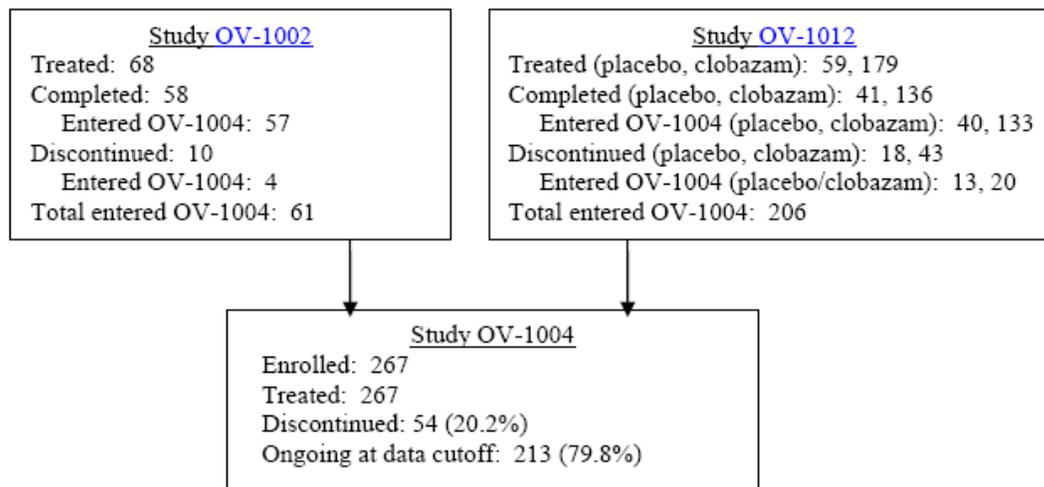
Demographic data for all subjects were re-collected upon entry into Study OV-1004. Neurological history data were only collected at screening in the previous blinded studies.

The majority of subjects were male (61.0%), White/Caucasian (65.9%), and not Hispanic or Latino (88.0%). Mean age at enrollment in Study OV-1004 was 11.1 years. Mean time since diagnosis of LGS was 4.3 years (range: 0-51 years). Most subjects (76.4%) did not have a history of status epilepticus. One-third of the subjects (33.3%) had a history of infantile spasms.

Disposition is summarized in Sponsor's Figure 5 below. All 267 enrolled subjects had participated in a previous blinded study, OV-1002 or OV-1012. Of all enrolled subjects, the majority had completed a previous blinded study (230/267, 86.1%) (OV-1004 Table 14.1.1.2). Most subjects (77.2%) had previously participated in Study OV-1012. Primary reasons for discontinuation from Study OV-1004 as of 01 July 2010 and reported for > 1.0% of subjects included subject/parent/caregiver request (7.9%), lack of efficacy (4.9%), adverse event (3.0%), and death (2.2%). The majority of enrolled subjects (79.8%) were ongoing in the study as of 01 July 2010.

Figure 3 Disposition of All Subjects in Study OV-1004 (Sponsor's ISE Figure 5)

Figure 5. Disposition of Subjects in Study OV-1004 – All Subjects



Source: [OV-1004 Tables 14.1.1.1](#) and [14.1.1.2](#)

Of the 13 placebo subjects who prematurely discontinued Study OV-1012 but enrolled in OV-1004, 9 had discontinued the blinded study due to lack of efficacy, 3 due to subject/parent caregiver request, and 1 due to AE. Of the 20 clobazam subjects who prematurely discontinued Study OV-1012 but enrolled in Study OV-1004, 12 prematurely discontinued the blinded study due to AE, 5 due to lack of efficacy, 2 due to subject/parent caregiver request, and 1 due to protocol violation. The 4 subjects who prematurely discontinued Study OV-1002 but enrolled in Study OV-1004 had prematurely discontinued the blinded study due to AE.

Extent of Exposure

Four categories of modal daily dose were defined: 0.25 mg/kg (> 0 to ≤ 0.375 mg/kg), 0.50 mg/kg (> 0.375 to ≤ 0.750 mg/kg), 1.00 mg/kg (> 0.750 to ≤ 1.250 mg/kg), and > 1.00 mg/kg (> 1.250 mg/kg).

In Study OV-1004, the mean modal and mean maximum doses were similar for subjects exposed ≥ 360 days (0.94 and 1.22 mg/kg/day), ≥ 180 days (0.90 and 1.16 mg/kg/day), and ≥ 1 day (0.88 and 1.13 mg/kg/day). The 2 most common modal doses were 0.5 mg/kg (> 0.375 to ≤ 0.750 mg/kg) and 1.0 mg/kg (> 1.250 mg/kg) (OV-1004). The majority of subjects (189/267 [70.8%]) have been exposed to clobazam for ≥ 12 months. The number of subjects exposed for ≥ 4 years, ≥ 3 years, and ≥ 2 years is 44 (16.5%), 48 (18.0%), and 94 (35.2%), respectively.

Selected Results from OV-1004:

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF DROP SEIZURES

For total subjects, median percent reduction in average weekly rate of drop seizures was 71.1% at Month 3 and increased across subsequent months to 91.6% at Month 24 (Table 16).

Similar results were observed through 12 and 24 months of treatment for the 12-month subset (subjects started clobazam ≥ 12 - < 24 months before data cutoff) and 24-month subset (subjects started clobazam ≥ 24 months before data cutoff), respectively.

Table 16 Percent Reduction in Average Weekly Rate of Drop Seizures in Study OV-1004 - Efficacy Analysis Set (Sponsor's ISE Table 25)

Table 25. Percent Reduction in Average Weekly Rate of Drop Seizures in Study OV-1004 – Efficacy Analysis Set

Month Parameter	Subject Subset		
	12-month N = 112	24-month N = 125	Total ¹ N = 267
Month 3	N = 107	N = 117	N = 252
Baseline median seizure rate (range)	27.0 (1, 1147)	53.0 (3, 1081)	33.0 (1, 1147)
Median percent reduction (range)	63.0 (-455, 100)	73.9 (-400, 100)	71.1 (-1575, 100)
Month 6	N = 99	N = 109	N = 232
Baseline median seizure rate (range)	29.0 (1, 1147)	43.0 (3, 1081)	33.0 (1, 1147)
Median percent reduction (range)	69.5 (-717, 100)	82.8 (-444, 100)	75.8 (-750, 100)
Month 9	N = 94	N = 101	N = 213
Baseline median seizure rate (range)	30.0 (1, 1147)	43.0 (3, 1081)	33.0 (1, 1147)
Median percent reduction (range)	78.9 (-450, 100)	87.5 (-517, 100)	81.3 (-517, 100)
Month 12	N = 72	N = 107	N = 180
Baseline median seizure rate (range)	29.5 (1, 1147)	43.0 (3, 1081)	33.0 (1, 1147)
Median percent reduction (range)	83.6 (-607, 100)	90.5 (-1430, 100)	86.1 (-1430, 100)
Month 18	N = 27	N = 97	N = 124
Baseline median seizure rate (range)	19.0 (2, 115)	40.0 (3, 1081)	33.0 (2, 1081)
Median percent reduction (range)	62.8 (-350, 100)	90.5 (-431, 100)	88.5 (-431, 100)
Month 24	N = 4 ²	N = 84	N = 88
Baseline median seizure rate (range)	19.5 (8, 94)	53.5 (3, 1081)	51.0 (3, 1081)
Median percent reduction (range)	97.9 (80, 100)	90.3 (-600, 100)	91.6 (-600, 100)

Note: Analysis includes subjects with both baseline and post-baseline data at each timepoint. Reduction in drop seizures was calculated as the weekly number of drop seizures during baseline (the last 7 non-missing diary days for subjects who received placebo in Study OV-1012 or the last 7 non-missing diary days from the baseline period of the previous blinded study for all other subjects) minus the number of seizures in the week preceding each study visit.

¹ Subjects with < 12 months of exposure to clobazam are only included in the Total column.

² Due to visit scheduling windows, 4 subjects in the 12-month subset had a Month 24 visit included.

Source: OV-1004 Table 14.2.1.1

FREQUENCY OF TREATMENT RESPONDERS WITH ≥ 25%, ≥ 50%, ≥ 75%, AND 100% REDUCTION IN AVERAGE WEEKLY RATE OF DROP SEIZURES

Although premature discontinuation of non-responding subjects in long-term studies may lead to overestimation of the efficacy of study drug, interim results for this study show that the percent of subjects with 100% reduction in average weekly rate of drop seizures was 28.6% at Month 3 and 39.8% at Month 24 (Table 17). The percent of Total subjects with ≥ 50% reduction in average weekly rate of drop seizures was 61.5% at Month 3 and 79.5% at Month 24. Similar results were observed through 12 and 24 months of treatment for the 12-month subset (subjects started clobazam ≥ 12 - < 24 months before data cutoff) and 24-month subset (subjects started clobazam ≥ 24 months before data cutoff), respectively.

Table 17 Categories of Improvement in Average Weekly Rate of Drop Seizures in Study OV-1004 - Efficacy Analysis Set

Month Improvement Category	Subject Subset		Total ¹ N = 267
	12-month N = 112	24-month N = 125	
Month 3, n (%)	N = 107	N = 117	N = 252
Any reduction	86 (80.4)	103 (88.0)	211 (83.7)
≥ 25% reduction	77 (72.0)	93 (79.5)	189 (75.0)
≥ 50% reduction	62 (57.9)	78 (66.7)	155 (61.5)
≥ 75% reduction	51 (47.7)	58 (49.6)	120 (47.6)
100% reduction	30 (28.0)	34 (29.1)	72 (28.6)
Month 6, n (%)	N = 99	N = 109	N = 252
Any reduction	78 (78.8)	99 (90.8)	197 (84.9)
≥ 25% reduction	75 (75.8)	94 (86.2)	187 (80.6)
≥ 50% reduction	67 (67.7)	87 (79.8)	168 (72.4)
≥ 75% reduction	46 (46.5)	63 (57.8)	119 (51.3)
100% reduction	30 (30.3)	33 (30.3)	67 (28.9)
Month 9, n (%)	N = 94	N = 101	N = 213
Any reduction	75 (79.8)	91 (90.1)	179 (84.0)
≥ 25% reduction	70 (74.5)	82 (81.2)	165 (77.5)
≥ 50% reduction	63 (67.0)	79 (78.2)	153 (71.8)
≥ 75% reduction	51 (54.3)	64 (63.4)	123 (57.7)
100% reduction	26 (27.7)	32 (31.7)	61 (28.6)
Month 12, n (%)	N = 72	N = 107	N = 180
Any reduction	57 (79.2)	97 (90.7)	155 (86.1)
≥ 25% reduction	51 (70.8)	96 (89.7)	148 (82.2)
≥ 50% reduction	46 (63.9)	93 (86.9)	139 (77.2)
≥ 75% reduction	41 (56.9)	72 (67.3)	113 (62.8)
100% reduction	22 (30.6)	37 (34.6)	59 (32.8)
Month 18, n (%)	N = 27	N = 97	N = 124
Any reduction	23 (85.2)	87 (89.7)	110 (88.7)
≥ 25% reduction	22 (81.5)	85 (87.6)	107 (86.3)
≥ 50% reduction	17 (63.0)	78 (80.4)	95 (76.6)
≥ 75% reduction	12 (44.4)	61 (62.9)	73 (58.9)
100% reduction	9 (33.3)	33 (34.0)	42 (33.9)
Month 24, n (%)	N = 4 ²	N = 34	N = 38
Any reduction	4 (100)	25 (89.3)	29 (89.8)
≥ 25% reduction	4 (100)	22 (85.7)	26 (86.4)
≥ 50% reduction	4 (100)	16 (78.6)	20 (79.5)
≥ 75% reduction	4 (100)	13 (75.0)	17 (76.1)
100% reduction	2 (50.0)	11 (39.3)	13 (39.8)

Note: Analysis includes subjects with both baseline and post-baseline data at each timepoint. Reduction in drop seizures was calculated as the weekly number of drop seizures during baseline (the last 7 non-missing diary days for subjects who received placebo in Study OV-1012 or the last 7 non-missing diary days from the baseline period of the previous blinded study for all other subjects) minus the number of seizures in the week preceding each study visit.

¹ Subjects with < 12 months of exposure to clobazam are only included in the Total column.

² Due to visit scheduling windows, 4 subjects in the 12-month subset had a Month 24 visit included.

Source: OV-1004 Table 14.2.1.2

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF TOTAL (DROP AND NON-DROP) SEIZURES
For Total subjects, median percent reduction in average weekly rate of total (drop and non-drop) seizures was 64.8% at Month 3, increased across subsequent months to 82.1% at Month 12, and remained generally stable through Month 24 (Table 18). Similar results were observed through 12 and 24 months of treatment for the 12-month subset (subjects started clobazam ≥ 12 - < 24 months before data cutoff) and 24-month subset (subjects started clobazam ≥ 24 months before data cutoff), respectively.

Table 18 Percent Reduction in Average Weekly Rate of Total (Drop and Non-drop) Seizures in Study OV-1004 - Efficacy Analysis Set (Sponsor's ISE Table 27)

Table 27. Percent Reduction in Average Weekly Rate of Total (Drop and Non-Drop) Seizures in Study OV-1004 – Efficacy Analysis Set

Month Parameter	Subject Subset		
	12-month N = 112	24-month N = 125	Total ¹ N = 267
Month 3	N = 110	N = 121	N = 260
Baseline median seizure rate (range)	42.0 (1, 1210)	69.0 (1, 1413)	54.5 (1, 1413)
Median percent reduction (range)	62.3 (-1483, 100)	70.0 (-600, 100)	64.8 (-1575, 100)
Month 6	N = 102	N = 113	N = 240
Baseline median seizure rate (range)	43.0 (1, 1210)	66.0 (1, 1413)	53.0 (1, 1413)
Median percent reduction (range)	70.0 (-733, 100)	75.0 (-1022, 100)	70.5 (-1022, 100)
Month 9	N = 97	N = 105	N = 221
Baseline median seizure rate (range)	43.0 (1, 1210)	64.0 (1, 1413)	54.0 (1, 1413)
Median percent reduction (range)	73.1 (-393, 100)	82.4 (-1182, 100)	78.4 (-1182, 100)
Month 12	N = 75	N = 111	N = 187
Baseline median seizure rate (range)	43.0 (1, 1210)	65.0 (1, 1413)	54.0 (1, 1413)
Median percent reduction (range)	72.5 (-607, 100)	83.3 (-2200, 100)	82.1 (-2200, 100)
Month 18	N = 29	N = 101	N = 130
Baseline median seizure rate (range)	36.0 (3, 144)	64.0 (1, 1413)	56.0 (1, 1413)
Median percent reduction (range)	62.5 (-182, 100)	82.6 (-3867, 100)	79.9 (-3867, 100)
Month 24	N = 4 ²	N = 87	N = 91
Baseline median seizure rate (range)	46.5 (23, 102)	64.0 (1, 1413)	61.0 (1, 1413)
Median percent reduction (range)	89.3 (36, 100)	81.3 (-3283, 100)	81.5 (-3283, 100)

Note: Analysis includes subjects with both baseline and post-baseline data at each timepoint. Reduction in total seizures was calculated as the weekly number of total seizures during baseline (the last 7 non-missing diary days for subjects who received placebo in Study OV-1012 or the last 7 non-missing diary days from the baseline period of the previous blinded study for all other subjects) minus the number of seizures in the week preceding each study visit.

¹ Subjects with < 12 months of exposure to clobazam are only included in the Total column.

² Due to visit scheduling windows, 4 subjects in the 12-month subset had a Month 24 visit included.

Source: [OV-1004 Table 14.2.2.2](#)

PERCENT REDUCTION IN AVERAGE WEEKLY RATE OF NON-DROP SEIZURE TYPES The seizures types reported by 25 or more subjects at baseline were atypical absence seizures, myoclonic seizures, tonic seizures, and tonic-clonic seizures. Among all subjects in the efficacy analysis set, median percent reductions in average weekly rate of non-drop seizures were 80.0%, 85.7%, and 87.5% for atypical absence seizures, myoclonic seizures, and tonic seizures, respectively, at Month 3 and were generally stable through 24 months of treatment (Table 19). For tonic-clonic seizures, the median percent reduction in average weekly rate of seizures was 46.4% at Month 3, increased to 83.3% at Month 6, and remained generally stable from Month 6 through Month 24.

Table 19 Percent Reduction in Average Weekly Rate of Non-Drop Seizures by Seizure Type in Study OV-1004 - Efficacy Analysis Set (Sponsor's Table 28)

Table 28. Percent Reduction in Average Weekly Rate of Non-Drop Seizures by Seizure Type in Study OV-1004 – Efficacy Analysis Set

Month Parameter	Seizure Type			
	Atypical Absence Seizures	Myoclonic Seizures	Tonic Seizures	Tonic-Clonic Seizures
Month 3	N = 51	N = 51	N = 47	N = 54
Baseline median seizure rate (range)	15.0 (1, 1410)	9.0 (1, 332)	11.0 (1, 110)	3.0 (1, 129)
Median percent reduction (range)	80.0 (-700, 100)	85.7 (-12800, 100)	87.5 (-250, 100)	46.4 (-2400, 100)
Month 6	N = 45	N = 47	N = 47	N = 53
Baseline median seizure rate (range)	15.0 (1, 1410)	9.0 (1, 332)	11.0 (1, 110)	3.0 (1, 129)
Median percent reduction (range)	100.0 (-2400, 100)	100.0 (-8700, 100)	100.0 (-318, 100)	83.3 (-4800, 100)
Month 9	N = 38	N = 39	N = 37	N = 50
Baseline median seizure rate (range)	15.5 (1, 1410)	9.0 (1, 332)	11.0 (1, 110)	3.0 (1, 129)
Median percent reduction (range)	100.0 (-767, 100)	100.0 (-300, 100)	100.0 (-929, 100)	100.0 (-9300, 100)
Month 12	N = 27	N = 31	N = 29	N = 42
Baseline median seizure rate (range)	16.0 (1, 1410)	8.0 (1, 135)	11.0 (1, 110)	3.0 (1, 129)
Median percent reduction (range)	100.0 (-63, 100)	100.0 (-250, 100)	100.0 (-325, 100)	81.5 (-3100, 100)
Month 18	N = 17	N = 20	N = 22	N = 37
Baseline median seizure rate (range)	16.0 (1, 1410)	10.0 (1, 135)	14.5 (1, 110)	3.0 (1, 129)
Median percent reduction (range)	100.0 (-230, 100)	100.0 (-950, 100)	96.1 (-475, 100)	100.0 (-6300, 100)
Month 24	N = 9	N = 6	N = 16	N = 25
Baseline median seizure rate (range)	12.0 (1, 1410)	7.5 (2, 135)	14.5 (1, 51)	2.0 (1, 40)
Median percent reduction (range)	95.0 (-107, 100)	100.0 (50, 100)	83.0 (-100, 100)	96.0 (-6100, 100)

Note: Analysis includes subjects with both baseline and post-baseline data at each timepoint. Reduction in non-drop seizures was calculated as the weekly number of non-drop seizures during baseline (the last 7 non-missing diary days for subjects who received placebo in Study OV-1012 or the last 7 non-missing diary days from the baseline period of the previous blinded study for all other subjects) minus the number of seizures in the week preceding each study visit.

Source: [OV-1004 Table 14.2.2.1](#)

COMPARISON OF THE NUMBER OF CONCOMITANT AEDS AT BASELINE AND FINAL EVALUATION

Rescue medications were not counted as AEDs upon enrollment into Study OV-1004 and were not summarized separately from concomitant AEDs.

Among subjects who were taking 3 or > 3 concomitant AEDs at baseline, 46.2% (36/78) and 43.5% (10/23), respectively, were taking fewer concomitant AEDs at the final evaluation as compared to baseline. Among subjects who were taking 1 or 2 concomitant AEDs at baseline, the majority (19/24 [79.2%] and 73/104 [70.2%], respectively) were taking the same number of concomitant AEDs at the final evaluation as compared to baseline.

Conclusions for OV-1004

The results of this long-term study support the persistence of the efficacy of clobazam in the adjunctive treatment of seizures associated with LGS.

Although premature discontinuation of non-responding subjects in long-term studies may lead to overestimation of the efficacy of study drug, specific findings from the total cohort of all subjects from this study are as follows:

- Median percent reduction in average weekly rate of drop seizures was 71.1% among all subjects at Month 3 and increased across subsequent months to 91.6% at Month 24.
- Median percent reduction in average weekly rate of total (drop and non-drop) seizures was 64.8% among all subjects at Month 3, increased across subsequent months to 82.1% at Month 12, and remained generally stable through Month 24.
- Median percent reductions in average weekly rate of specific types of non-drop seizures were 80.0%, 85.7%, and 87.5% for atypical absence seizures, myoclonic seizures, and tonic seizures, respectively, at Month 3 and were generally stable through 24 months of treatment. For tonic-clonic seizures, the median percent reduction in average weekly rate of seizures was 46.4% at Month 3, increased to 83.3% at Month 6, and remained generally stable from Month 6 through Month 24.
- The majority of subjects were assessed by the physician (range: 66.3-82.3%) and by the parent/caregiver (range: 61.5-80.5%) as much improved or very much improved at Months 3, 6, 9, 12, 18, and 24.

Reviewer Comments:

Although this study is uncontrolled, it suggests that there was sustained efficacy and tolerability for the majority of patients who finished Studies OV-1002 and 1012.

86 Review of Efficacy

Efficacy Summary

These Phase 2/3 studies demonstrate that treatment with low (target dose of 0.25 mg/kg of clobazam [up to a maximum daily dose of 10 mg]), medium (target dose of 0.5 mg/kg of clobazam [up to a maximum daily dose of 20 mg]), and high (target dose of 1.0

mg/kg of clobazam [up to a maximum daily dose of 40 mg]) doses of clobazam is effective as adjunctive therapy in the treatment of seizures associated with LGS in subjects ≥ 2 years of age.

The pivotal study (OV-1012) provides robust statistical and clinical evidence for the efficacy of clobazam in the adjunctive treatment of drop seizures. The medium-dose and high-dose of clobazam met the criterion for robust statistical significance ($p \leq 0.01$) versus placebo. In addition, the low-dose group was statistically significantly superior ($p \leq 0.05$) to placebo. A statistically significant linear trend ($p < 0.0001$) of increasing efficacy with increasing dose was observed. All clobazam dose groups showed statistical superiority (medium-/high-dose groups $p \leq 0.01$; low-dose group $p \leq 0.05$) to placebo in average weekly rate of total seizures (drop and non-drop). In addition, the average weekly rate of non-drop seizures for all dose groups was reduced in a dose-dependent manner compared with placebo. These results are supported by those from Study OV-1002 and by the open-label extension Study OV-1004, in which efficacy has been observed for as long as 24 months of treatment with clobazam. Both physicians and parents/caregivers assessed that clobazam treatment was associated with global improvements in subjects' overall symptoms.

Tables 20 and 21 below from the ISE of the NDA submission summarize efficacy from the two studies, first showing efficacy with regard to drop seizures in Table 20 (the primary endpoint) and second showing efficacy with regard to both drop and non-drop seizures (Table 21). Additional discussion is available from the statistical review.

Table 20 Percent Reduction in Average Weekly Rate of Drop Seizures from Baseline to the Maintenance Period of Double blind Phase - MITT Population

Table 2: Percent Reduction in Average Weekly Rate of Drop Seizures from Baseline to the Maintenance Period of Double-blind Phase – MITT Population

Variable Statistic	Study OV-1002		Study OV-1012			
	Clobazam Dose Level		Placebo N = 57	Clobazam Dose Level		
	Low N = 29	High N = 32		Low N = 53	Medium N = 58	High N = 49
Baseline drop seizure rate	142.0	209.1	97.8 (170.7)	99.8 (206.0)	60.5 (122.5)	105.2 (163.3)
Mean (SD)	(190.2)	(229.2)	35.5	29.2	22.5	46.4
Median	66	97	2, 920	2, 1077	2, 798	2, 856
Range	5, 661	8, 924				
Percent reduction during the maintenance period ¹						
Mean (SD)	10.1 (122.3)	85.2 (17.1)	12.5 (72.7)	41.6 (46.8)	47.8 (62.0)	69.5 (39.7)
Median	29	93	23.2	46.7	57.9	86.5
Range	-531, 100	48, 100	-374, 100	-119, 100	-262, 100	-39, 100
p-value: comparison to placebo ²				0.0120	0.0015	< 0.0001
p-value: comparison between high and low dose		< 0.0001				

Table 21 Percent Reduction in Average Weekly Rate of Total (Drop and Non-drop) Seizures from Baseline to the Maintenance Period of Double blind Phase - MITT Population

Table 2: Percent Reduction in Average Weekly Rate of Total (Drop and Non-drop) Seizures from Baseline to the Maintenance Period of Double-blind Phase– MITT Population

Variable Statistic	Study OV-1002		Study OV-1012			
	Clobazam Dose Level		Placebo N = 57	Clobazam Dose Level		
	Low N = 29	High N = 32		Low N = 53	Medium N = 58	High N = 49
Baseline drop seizure rate	153.3	216.6	117.1	131.1	111.5	128.7
Mean (SD)	(185.6)	(229.4)	(178.9)	(224.2)	(224.7)	(184.5)
Median	88.1	105.2	46.8	45.5	36.6	80.6
Range	9, 665	8.5, 927	4, 920	4, 1125	3, 1465	2, 864
Percent reduction during the maintenance period ¹						
Mean (SD)	19.1 (64.3)	85.2 (17.1)	10.1 (55.2)	36.8 (48.1)	42.2 (89.6)	66.2 (40.0)
Median	27.1	86.2	11.3	43.1	62.1	82.8
Range	-129, 100	29, 100	-189, 100	-155, 100	-523, 100	-49, 100
p-value: comparison to placebo ²				0.0414	0.0044	< 0.0001
p-value: comparison between high and low dose ³		< 0.0001				

Reviewer Comment:

Because only one study was presented as pivotal (OV-1012) and only one study as supportive, (OV-1002), the two studies' results are presented individually in section 5.3 of this review.

6.1.8 Subpopulations

Subgroup analyses in the pivotal study OV-1012 demonstrated efficacy regardless of age, gender, race, ethnicity, region, or concomitant treatment with valproate or lamotrigine. Efficacy was also demonstrated after adjusting for LGS disease severity in an analysis that accounted for age of onset of LGS, history of status epilepticus, history of infantile spasms, and baseline seizure rate.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Clobazam is effective in the adjunctive treatment of seizures associated with LGS. Efficacy results were dose dependent in both double-blind studies. Robust efficacy with respect to drop seizures was observed in Study OV-1012 at the high and medium doses; statistically significant efficacy was also seen in the low-dose group. Moreover, all clobazam dose groups showed statistical superiority to placebo in average weekly rate of total seizures (drop and non-drop). In addition, the average weekly rate of non-drop seizures for all dose groups was reduced in a dose-dependent manner compared with placebo. These results were supported by Study OV-1002, in which the high-dose group had significantly greater efficacy than the low-dose group on drop seizures, total seizures, and non-drop seizures.

The similarities of results between the common dose levels in these 2 studies demonstrate the robustness of the results and give a clear indication of the extent of the benefit and relationship to dose.

In Study OV-1012, subjects who were randomized to receive an active treatment of clobazam and weighing ≤ 30 kg began treatment with 5 mg of clobazam, while subjects weighing > 30 kg began treatment with 5 or 10 mg clobazam. For the subjects randomized to low-, medium-, or high-dose groups, the protocol-specified dosing paradigm was implemented using fixed doses in order to achieve a target exposure during the maintenance period of approximately 0.25, 0.5, or 1.0 mg/kg/day, respectively. After initiation of therapy, actual doses were escalated in 5, 10, or 15 mg increments on a weekly basis until the assigned target dose was attained (maximum daily dose of 10, 20, or 40 mg/day, respectively). Due to the wide variability of individual weights across the population of subjects, the actual exposures (mg/kg) for individual subjects varied with respect to the predefined dose group. For simplicity of dosing instructions, dosing by total daily dose (mg/day) rather than an approximate target exposure (mg/kg) is recommended.

The dosing recommendations are as follows:

-  (b) (6)
-  (b) (6)

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

Adequate Duration of Treatment Period in Study OV-1012 for Assessment of Tolerance

Evaluation of effectiveness over time (ie, percent reduction from baseline in average weekly rate of drop seizures, and frequency of treatment responders over time) in Study OV-1012 supports the tolerance analyses by demonstrating, on average, maintenance of substantial response (ie, $\geq 50\%$ reduction from baseline in average weekly rate of drop seizures) in the clobazam treatment groups compared with placebo.

In most published studies, the majority of the subset of subjects who demonstrate tolerance to clobazam do so within the first 3-4 months of therapy. Therefore, a 15-week treatment period, as in Study OV-1012, is adequate to estimate the magnitude of tolerance, although it is likely that some additional subjects would develop diminution of response or tolerance if followed long enough. It is not feasible to carry out a placebo-controlled clinical trial in a severe epilepsy syndrome such as LGS to rigorously quantify the extent of tolerance over years of use.

Development of Tolerance in Study OV-1012

There are no widely applied definitions or methods of assessing tolerance in clinical studies of AEDs. Generally, tolerance is thought to occur when a patient who initially demonstrates a response to a drug experiences a loss or a lessening of that response with repeated administration of the drug at a fixed dose. However, it is generally not possible from clinical trial data to distinguish tolerance from a number of potential confounding factors related to clinical course. Some of the most common confounding factors are disease progression, random fluctuations in the expression of the disease, intercurrent illness, non-compliance, and changes in dose of the drug of interest or of concurrent medications.

Because of fluctuations in seizure frequency over time in LGS, as well as the changing seizure types that occur as part of the natural history of the disease, it is necessary to compare a drug-treated group with a placebo-treated or untreated control group to estimate the development of tolerance to a new AED added to a patient's regimen. When population statistics are examined, comparing the first 4 weeks of the maintenance period to the last 4 weeks with respect to mean reduction from baseline in average weekly rate of drop seizures, there is less decline in seizure control over time in the clobazam groups than the placebo group, suggesting that most of the fluctuations seen in the clobazam groups are due to the nature of the underlying epilepsy syndrome.

To better quantify tolerance in Study OV-1012, two prespecified definitions of tolerance were used. Tolerance was defined as achievement of $\geq 50\%$ reduction in average weekly rate of drop seizures from baseline to the first 4 weeks of the maintenance

period, with a return to the baseline seizure rate before end of the maintenance period or discontinuation due to a lack of efficacy. A second definition of tolerance considered the first 8 weeks of the maintenance period.

The percent of subjects experiencing tolerance was small and similar among treatment groups. Based on the first definition, this percent ranged from 5.3% to 9.5% across clobazam groups and was 5.6% in the placebo group. Based on the second definition, tolerance was only noted in the placebo (1/20 [5.0%]) and medium-dose (3/38 [7.9%]) treatment groups.

An additional analysis of tolerance based on responder analyses showed that the percent of clobazam subjects with no change or improvement from the first 4 weeks to the last 4 weeks of the maintenance period in Study OV-1012 was greater than the percent of clobazam subjects who worsened or withdrew in each treatment group. In addition, the percent of clobazam subjects who worsened or withdrew was lower in each dose group compared to placebo.

Any observed diminution in efficacy response or apparent tolerance in association with clobazam administration can be managed with appropriate monitoring and dose adjustments, if necessary.

Persistence of Efficacy as an Indirect Measure of Tolerance

Clinically, the most relevant information in determining the utility of an AED is the probability that an individual patient will derive long-term benefit from the drug. The failure to derive long-term benefit can have multiple causes, including lack of efficacy, intolerable side effects, development of tolerance, fluctuations in seizure frequency interpreted as lack of efficacy and failure to test the drug at an adequate dose or for an adequate duration of treatment. Assessment of efficacy over time in the long-term study demonstrated that the majority of subjects, 80% or more, who remained in Study OV-1004 maintained a substantial reduction (ie, $\geq 50\%$ reduction from baseline in average weekly rate of drop seizures) in seizure frequency for as long as 24 months after starting clobazam.

Moreover, of the 267 subjects randomized to Studies OV-1002 and OV-1012 who entered into Study OV-1004 beginning in December 2005, 213 (80%) continued taking clobazam as of 01 July 2010, indicating that benefit from clobazam treatment is perceived for the majority of subjects.

Although a small proportion of subjects showed a diminution of response, or tolerance to the anti-epileptic effects of clobazam in the pivotal study (OV-1012), persistence of efficacy was demonstrated in Study OV-1004. A high retention rate of subjects was

observed in this long-term study and maintenance of the efficacy was observed of clobazam over time in the adjunctive treatment of seizures associated with LGS.

6.1.11 Additional Efficacy Issues/Analyses

None

7 Review of Safety

The Review of Safety was done as a separate review by Dr. Gerard Boehm.

8 Postmarket Experience

Clobazam is a 1,5–benzodiazepine approved for the treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries worldwide. It is not currently approved in the United States for any indication.

In Periodic Safety Update Reports submitted to the European Medicines Agency by Aventis from November 1994 to February 2010, there were over 3.4 million patient years of exposure.

The Review of Safety including post-marketing experience was done as a separate review by Dr. Gerard Boehm.

9 Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

Pending from Clobazam Review Team.

9.3 Advisory Committee Meeting

None required.

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/s/

PHILIP H SHERIDAN
10/04/2011

NORMAN HERSHKOWITZ
10/05/2011

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

NDA: 202067
Drug: Clobazam (Onfi)
Route: Oral
Indication: Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients \geq 2 years of age.
Sponsor: Lundbeck
Submission Date: 12/23/10
Review Date: 8/31/11
Reviewer: Sally Usdin Yasuda, Safety Team Leader
Division of Neurology Products

1. Background

Clobazam (a 1, 5 benzodiazepine) has been proposed as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients \geq 2 years of age. The mechanism of action is not fully understood but is presumed to be due to activity as a positive allosteric modulator at GABA (A) receptors resulting in enhanced chloride currents mediated via GABA. According to the Sponsor, clobazam has been approved outside of the United States (US) for almost 40 years. It is approved for treatment of anxiety disorders, epilepsy, and similar indications in over 80 countries, with an estimated (b) (4) person-years of use. For LGS, the proposed initial dose for patients \leq 30 kg body weight is 5 mg daily to be titrated to 10-20 mg daily, and the proposed initial dose for patients $>$ 30 kg is 10 mg daily to be titrated to 20-40 mg daily.

In terms of the clinical pharmacology of clobazam, the T_{max} ranges from 0.5 to 4 hours. It is extensively metabolized, primarily by CYP3A4 as well as by CYP2C19 and CYP2B6. N-desmethyloclobazam (N-CLB) is an active metabolite and has exposure greater than 10% of the circulating parent. It is metabolized primarily by CYP2C19. The median half-lives of clobazam and N-CLB are estimated to be 36 and 79hr, respectively. CYP2C19 poor metabolizers (PMs) have approximately 5-fold higher exposure to N-CLB than to extensive metabolizers (EMs) or intermediate metabolizers (IMs). In a mass balance study, approximately 82% of the dose was recovered in the urine, with clobazam representing approximately 2% of the total.

This memorandum primarily summarizes the findings of Dr. Jerry Boehm's primary safety review of the clobazam NDA. Please refer to Dr. Boehm's review for more detail.

2. Summary of Findings from the Safety Review

2.1 Sources of Data, Exposure, and Demographics

**Safety Team Leader Memo
NDA 202067**

The Sponsor's submission summarized safety data from 56 clinical trials. These include Phase 1 trials (7 trials in healthy adults including a thorough QT study and 1 trial in subjects with renal impairment)¹, Lundbeck Phase 2/3 trials in LGS (2 randomized, double blind, controlled trials and 1 ongoing open label extension), and a Legacy Epilepsy Trial in children (6 months – 17 y.o.) with partial epilepsies or generalized tonic-clonic seizures (conducted by the previous sponsor in the early 1990s). The safety database also includes 44 Legacy Psychiatry trials (with doses from 10 mg to 120 mg/day) conducted over 40 years ago. Dr. Boehm notes that the data from the Legacy Psychiatry trials are limited as 31 have CRFs and 13 do not, data cannot be verified due to lack of access to trial site/personnel, and at the time of the trials there was no regulatory definition of SAEs and these events were not prospectively reported. In the safety analysis, the Phase 1 trials have been pooled; the Phase 2/3 trials have been analyzed separately as well as pooled.

The characteristics of the Lundbeck Phase 2/3 trials are briefly described as follows as summarized by Dr. Boehm. OV-1002 was a randomized, double-blind, low dose (0.25 mg/kg) vs high dose (1.0 mg/kg) adjunctive treatment trial in patients aged 2-30 years with LGS. The study included a 4 week baseline phase followed by a 3 week titration phase and a 4 week maintenance phase. OV-1012 was a double-blind, adjunctive treatment trial that randomized patients with LGS, aged 2-60 years old, to placebo or one of 3 clobazam doses (0.25 mg/kg, 0.5 mg/kg, or 1.0 mg/kg). The trial included a 4 week baseline phase followed by a 3 week titration phase and a 12 week maintenance phase. At the end of either trial, patients were either tapered off clobazam or enrolled in OV-1004. OV-1004 is the ongoing open label extension in which subjects were allowed to enroll if in the preceding trial they did not have a serious or severe AE that the investigator felt was due to clobazam. For subjects from OV-1012, clobazam was started at 0.5 mg/kg (not to exceed 40 mg/day) and the maximum target dose is 2.0 mg/kg (up to 80 mg/day). For subjects from OV-1002, an unblinded physician determined whether to maintain the dose that the patient was taking or to adjust the dose.

The Legacy Epilepsy Trial 301 was a randomized double-blind, active controlled monotherapy trial of 1 year in duration conducted in children (6 months to 17 years) with partial epilepsies or generalized tonic clonic seizures, conducted in the early 1990s in Canada. Study medication was introduced over 1-3 weeks to a daily target dose of clobazam 0.5 mg/kg, carbamazepine 10 mg/kg, or phenytoin 5 mg/kg. If subjects were receiving an AED at study entry, the AED was discontinued during the initial 3 week period. Investigators were allowed to increase or decrease study medication according to clinical response.

¹ There were 14 additional Phase 1 trials conducted by the previous sponsor that are not reviewed in the body of the ISS. Lundbeck reviewed the study reports and notes no deaths, SAEs, or AEs of special interest and that somnolence was the most commonly reported AE.

According to Dr. Boehm’s review, the NDA includes 2236 subjects exposed to clobazam. However, exposure information was unknown in the Legacy Psychiatry studies in 389/1484 patients, leaving only 1095 patients with exposure information in those studies. Exposure is shown in the table below from Dr. Boehm’s review.

Table 3. Estimated Clobazam Exposures in Unique Subjects (30 November 2010)

Duration of clobazam exposure	Total	Phase 1 Studies	Phase 2/3 LGS Studies	Legacy Epilepsy Study 301	Legacy Psychiatry Studies ¹
At least 1 dose	1847	333	300	119	1095*
6 months	357	N/A	253	80	24
12 months	239	N/A	197	45 ²	1
24 months	95	N/A	100	N/A	N/A

120 day Safety Update, p.17, NA = not applicable

*Total includes only those subjects with exposure data

In the Phase 2/3 trials, subjects were exposed to clobazam at doses in the sponsor’s proposed recommended range (considering either the modal or maximum dose) as shown in Table 4 of Dr. Boehm’s review. In the Legacy Epilepsy trial, 80 patients were exposed for 6 months at a mean modal dose of 0.673 mg/kg, of which 3 were in the low dose group (0.25 mg/kg up to 10 mg/day), 57 were in the medium dose group (0.5 mg/kg up to 20 mg/day), 16 were in the high dose group (1 mg/kg, up to 40 mg/day), and 4 were in the maximum dose group (> 1 mg/kg up to 80 mg/day). *Considering only the Lundbeck conducted Phase 1-3 trials, the exposure falls substantially short of ICH requirements of 1500 subjects total and short of the requirement of 300 subjects for 6 months, but meets the minimum requirement of 100 subjects for 1 year. The Legacy Epilepsy trial contributes to the database that fulfills the requirement for 300 subjects for 6 months.* The largest contribution to the total exposure is from the Legacy Psychiatry trials (n=1484; exposure information was only available for 1095 subjects in these trials). The 1095 subjects in those trials were exposed to doses in the range proposed for LGS. *Considering the Lundbeck Phase 1-3 studies and the Legacy Epilepsy studies (n= 752) as well as the Psychiatry Legacy studies, the database fulfills the requirement of 1500 subjects total, although as noted above, there are limitations to the Psychiatry trials as noted above, including the lack of identification of SAEs. The safety database is also supplemented by the postmarketing experience.*

Demographics –

In Phase 1 trials, the age range was 18-74 years. In the Phase 2/3 trials, the age range was 1.8 to 54 years. The mean age in OV-1002 was approximately 9 years, and in OV-1012 the mean for each dosage was approximately 9-11 years. In the Legacy Epilepsy trial the average age was approximately 8 years. The percentage of males in each study was slightly higher than the percentage of females, and was 59-64%. In the Phase 1-3 trials, subjects were predominately white (≥ 58%). Race data was not recorded in the Legacy Epilepsy study. In

the OV-1012 approximately 70% of the subjects were from the US, approximately 23% from India, and approximately 7% from the rest of the world. In OV-1002, all subjects were from the US.

2.3 Significant Safety Findings

2.3.1 Deaths

Dr. Boehm notes that there were 9 deaths in the clobazam exposed subjects, all during the open label extension trial OV-1004. There was 1 death reported from the legacy epilepsy trial 301 in a subject on carbamazepine and 1 in the legacy psychiatry trials in a subject taking placebo.

Of the 9 deaths in OV-1004, 5 were male and 4 were female. The ages were 4 (n=2), 5, 7, 8, 12, 19, 22, and 36 years. The total daily doses at the time of the event were 10 mg, 20 mg, 30 mg (n=2), 35 mg (n=2), 40 mg, and 50 mg (n=2). In 3 cases the reported cause of death was pneumonia. Among those cases, 1 patient had an AE of somnolence noted approximately 1 month prior to, and was continuing at the time she developed pneumonia. The other 2 cases did not have an AE of somnolence at the time of pneumonia. One additional patient died while receiving hospice care following hospitalization for pneumonia and dehydration. Three patients died at home and had no clearly identified cause of death (death n=2, epilepsy). One patient died during hospitalization for seizures with reported cause of death respiratory failure. One patient died during hospitalization for hematoma and urosepsis. Dr. Boehm notes that all of the subjects had severe neurological disabilities. Please refer to Dr. Boehm's review for details of these deaths.

Dr. Boehm notes that although there were 5 deaths with respiratory etiologies, the patients had underlying medical conditions (neurological disabilities, documented aspiration, gastroesophageal reflux, feeding tubes, etc) putting them at high risk of respiratory disorders and infections. *I agree with Dr. Boehm that it is not possible to assess the role of clobazam in these deaths that all occurred in the open label study.*

2.3.2 Other Serious Adverse Events

SAEs in the Phase 1 Trials – There were no SAEs reported in the Phase 1 trials.

Overview of SAES in the Phase 2/3 Trials – Dr. Boehm notes that 34% (103/300) of clobazam subjects experienced one or more treatment emergent SAEs. The System Organ Class (SOC) grouping with the most SAEs was Infections and Infestations (17.3%, n=52). Dr. Boehm has provided a list of SAEs reported by at least 2 clobazam subjects in the pooled Phase 2/3 trials (OV-1002, OV-1012, and open label extension OV-1004). The most frequent was pneumonia (8.7%, n=26). There were 2 SAEs of pancreatitis, described below. There was 1 SAE of hepatic enzyme increased.

No subjects experienced SAEs of aplastic anemia, agranulocytosis, Stevens Johnson Syndrome Toxic epidermal necrolysis, acute renal failure, acute liver failure, angioedema, anaphylaxis, pancytopenia, or rhabdomyolysis.

SAEs in the Phase 2/3 Randomized Controlled Trials (RCTs) – In OV-1002, 6.3% (2/32) of the clobazam low dose patients experienced an SAE compared to 8.3% (3/36) of the high dose patients. In OV-1012, 3.4% (2/59) of patients in the placebo group experienced an SAE compared to 5.2% (3/58) in the low dose clobazam group, 9.7% (6/62) in the medium dose clobazam group, and 8.5% (5/59) in the high dose clobazam group. Pneumonia was the most frequent SAE in OV-1012 and (3.4%, 2/58 in the low dose group, 3.2%, 2/62 in the medium dose group, and 1.7%, 1/59 in the high dose group), and there were no SAEs of pneumonia in OV-1002.

Dr. Boehm has reviewed the following select SAEs of interest in the Phase 2/3 RCT safety population and I summarize those below:

Adverse Drug Reaction – Subject 0058-7032 had a serious AE coded to the preferred term “Adverse drug reaction”. On study day 7, this 3 y.o. male developed an erythematous rash on his chest, extremities, and chin, with no mucosal involvement. One lesion was reportedly blistered on day 9. He was admitted to a hospital for a day and treated with IV fluids, diphenhydramine, and cetirizine. Lamotrigine (started approximately 7 months prior to taking clobazam) and clobazam were stopped on the day 7. The rash resolved on study day 12. As lamotrigine had been taken for 7 months, this was unlikely due to lamotrigine. *The role of clobazam cannot be ruled out.*

Drug Toxicity – Subject 0822-7079, a 9 y.o. male, experienced a SAE that was coded to the preferred term “Drug Toxicity”. He reportedly tolerated the drug well until Study Day 13 when he received the study drug in the wrong sequence (the number of tablets incorrectly administered was not documented) and then became restless and had imbalance. He was not able to walk properly and had a tendency to fall while walking, and had extreme somnolence. The subject gradually improved over 2 days after the study drug regimen was stopped.

Thrombocytopenia – Three subjects experienced 4 SAEs coded to “thrombocytopenia” and as Dr. Boehm notes, the case narratives identified confounding factors for these events. Subject 0803-7132 was a 2 y.o. female hospitalized for thrombocytopenia on Study Day 87. The subject was also taking sodium valproate at the time of the event. Platelet counts at screening were 118 GI/L, below the normal range (252-582 GI/L) and had decreased to 38 GI/L by Day 52 and to 13 GI/L on Day 87. Valproic acid concentrations during the study increased from 672 umol/L at screening to 938 umol/L on Day 88 (ULN = 700 umol/L). Study drug and sodium valproate were discontinued on Day 87. Platelets were given on Study Day 88 and the thrombocytopenia resolved on Day

97. Thrombocytopenia is a Warning in the valproic acid labels and appears to be related to concentration. Subject 0008-0407, a 6 y.o. male, developed macrocytic anemia (MCV of 105 fL, normal: 75-94 fL) and thrombocytopenia (platelet count 65×10^9 , normal $150-450 \times 10^9$) on Day 198 while receiving 20 mg clobazam and being hospitalized for pneumonia. The subject was also taking valproic acid. Valproic acid dosing was held for 3 doses and study drug dose was interrupted for 1 day. The events resolved on Day 207. Of note, the valproic acid labels state that in some patients platelet counts normalized while patients continued treatment. Subject 0038-8002, an 11 y.o. female, was hospitalized 4 times for vomiting; convulsion and varicella; *klebsiella* cystitis; and pancreatic pseudocyst (x2). She was on multiple other medications that are reportedly associated with thrombocytopenia, including valproic acid. The hospitalizations were associated with varying degrees of thrombocytopenia that in 3 cases resolved without discontinuation of clobazam. The thrombocytopenia in the 4th hospitalization was reported ongoing as of the data cut off date for the study. *I agree with Dr. Boehm that these cases are confounded.*

Pancreatitis - Subject 0003-0208 was a 7 y.o. male hospitalized with septic shock secondary to gastric perforations after elective surgery for hiatal hernia. Study drug was temporarily interrupted but resumed the day following surgery (Day 621). On Day 634 he was diagnosed with pancreatitis. Concomitant medications included valproic acid that has a boxed warning regarding pancreatitis. Study drug continued with the dose unchanged. The event resolved on Day 652. Subject 0017-8102 was an 11 y.o. male who was hospitalized for Guillain-Barre syndrome on Day 28 and diagnosed with pancreatitis on Day 37. Study drug was interrupted on Day 28, restarted on Day 29, interrupted on Day 30 and restarted on Day 51. Pancreatitis resolved on Day 71 and Guillain-Barre resolved on Day 72. The subject was taking multiple concomitant medications including furosemide and valproic acid, both of which have been associated with pancreatitis. Of note, according to the valproic acid labeling, pancreatitis can occur after several years of use of valproic acid. *In both cases, pancreatitis seems unlikely to be related to the use of clobazam.*

Renal Tubular Necrosis – Subject 0012-7023, a 7 y.o. male, experienced renal tubular necrosis while hospitalized for pneumonia and septic shock. The events resolved with clobazam dose unchanged and the patient continued in the study.

SAEs from Legacy Trials – In the Legacy epilepsy trial 301, 10% (12/119) of clobazam subjects and 32% (37/116) of control subjects experienced one or more SAEs. Convulsion (n=7) and self injurious ideation (n=2) were the only SAEs reported by more than 1 clobazam subject. The other SAEs reported for clobazam subjects were drug ineffective, pyrexia, gastroenteritis, pneumonia, diagnostic procedure, EEG, muscle twitching, muscular weakness, astrocytoma, complex partial seizures, dysarthria, facial paralysis, somnolence, status epilepticus, abnormal behavior, breathing related sleep disorder, depressed, mood, depression, disturbance in social behavior, respiratory distress, sleep

apnea, stridor, tonsillar hypertrophy, tendon transfer, and tonsillectomy. In the Legacy Psychiatry trials, SAEs were not prospectively reported. The Sponsor identified 5 SAEs (out of 1484 clobazam subjects) by reviewing CSRs and CRFs for hospitalizations. Subject 0001-0004 (Study 315) experienced jaundice with increased LFTs including total bilirubin and alkaline phosphatase. He had a history of alcoholism and the liver biopsy was reportedly consistent with alcoholic cirrhosis. The reasons for hospitalization in the remaining 4 patients were worsening of underlying psychiatric condition (n=2), appendicitis, and reason unknown.

2.3.3 Dropouts

In the Phase 1 studies, 6.3% (n=22) of clobazam subjects discontinued prematurely. AE was the most common reason for discontinuation (3.7%, n=13). Other reasons were protocol violation (n=1), withdrew consent (n=7), and other (n=1). Adverse events leading to discontinuation were transaminase increased (n=3), delirium (N=3), somnolence (n=3), dizziness (n=2), depressed mood, libido decreased, erectile dysfunction, insomnia, dysarthria, gait disturbance, and mental status changes. In the subjects with transaminase increased, the increased ALT and AST were in the range of 120-278 U/L, the elevations began within 14 days of starting study drug, were not accompanied by increases in bilirubin, and returned to normal limits within 2 weeks of discontinuing study drug.

In the Phase 2/3 trials, AE was the most common reason for premature discontinuation for clobazam subjects in the controlled trials; it was the most common reason for premature discontinuation in placebo subjects in OV-1002. In all three clobazam Phase 2/3 trials, 16% (46/300) of patients had one or more AEs that led to discontinuation. In OV-1002 those AEs leading to discontinuation in more than 1% of the patients were somnolence, aggression, lethargy, ataxia, fatigue, and insomnia. These were also among the most common in Phase 2/3 trials overall. Overall discontinuations due to AEs in the controlled trials suggested a dose response, but I agree with Dr. Boehm that the small number of events does not provide robust evidence of dose response for any particular AE leading to discontinuation. One patient in OV-1004 discontinued due to rash and will be discussed under *Drug Reaction with Eosinophilia and systemic symptoms* (DRESS) in "Significant Adverse Events".

In the Legacy Epilepsy trial (301) 10.9% (13/119) of clobazam patients and 29.3% (34/116) of active control patients discontinued for AEs. The AEs reported for the clobazam subjects who discontinued prematurely were abnormal behavior (n=3), drug ineffective (n=3), irritability (n=2), weight increased (n=2), abdominal pain, abdominal pain upper, aggression, appendicitis, balance disorder, convulsion, coordination abnormal, depression, disturbance in attention, drooling, fatigue, headache, hypersomnia, inappropriate affect, lethargy, nausea, personality change, psychomotor hyperactivity, poor quality sleep, rash, retching, somnolence, and vomiting. There were also withdrawals (3 clobazam subjects, 3 carbamazepine subjects, and 1 phenytoin subject) with a constellation of

symptoms of behavioral deterioration (aggressive agitation, self-injurious behavior, insomnia, and incessant motor activity) referred to as “catastrophic personality disintegration” (CPD), a syndrome only described in the literature by one of the investigators in the trial. CPD resolved after discontinuation of clobazam.

In the Legacy Psychiatry trials, discontinuations due to AEs that occurred in at least 2 clobazam subjects and that occurred more frequently compared to placebo were somnolence (3%), confusional state (1%), depression (1%) in the controlled trials in the US/Canada (there were no occurrences in the placebo group), and asthenia (0.7%), fatigue (0.5%), irritability (0.7%), somnolence (1.5%), syncope (0.3%), depression (0.7%), erectile dysfunction (0.3%), and urticaria (0.3%) in the non-CRF trials. Thirty patients discontinued due to AEs but did not have a corresponding term identified for the event.

2.3.4 Significant Adverse Events

The Sponsor evaluated these specific AEs for clobazam by considering the characteristics of the intended treatment population, and the AEs associated with the use of other AEDs.

Seizure-related AEs –

Dr. Boehm has summarized the seizure risk data in the NDA. In OV-1012, the risk of developing a new seizure type was 3.4% in the placebo group and 3.4% in the clobazam group overall (low dose 1.7%, medium dose 3.2%, and high dose 5%). In OV-1002 3.1% of low dose and 8.3% of high dose patients developed a new seizure type during the trial, as did 7% in the open label extension OV-1004. *I agree with Dr. Boehm that there is not strong evidence to support that clobazam increased the risk of developing a new seizure type. Based on Dr. Boehm’s review of the Sponsor’s presentation of seizure frequency from AEs and analysis of seizure diaries, I also agree that there was not strong evidence to support a conclusion that clobazam is associated with increased seizure frequency.*

Pneumonia - There were no pneumonia-related AEs in the Phase 1 trials or Legacy Psychiatry trials and 1 pneumonia-related AE in the Legacy Epilepsy trial. According to Dr. Boehm’s review, the risk for all pneumonia-related AEs in clobazam patients in the LGS RCTs was 4% (10/247). In the placebo controlled trial OV-1012, there were 8 (8/179, 4.5%) pneumonia-related AEs in clobazam patients (all SAEs, 2 low dose, 2 medium dose, 4 high dose) and 1 pneumonia-related SAE in a placebo patient (1/59, 1.7%). In OV-1002, there were 2 nonserious pneumonia-related AEs (both high dose, 2/68, 3.9%). In the open label extension OV-1004, 46 patients experienced one or more pneumonia-related AEs (15%, 46/300). A time to event analysis in Phase 2/3 trials, shown in Dr. Boehm’s review, suggests that the pneumonia AE risk appeared fairly constant through the first 500 days of treatment, with a plateau after that point.

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The Sponsor's logistic regression analysis attempted to identify covariates that predicted pneumonia events in clobazam treated patients. The sponsor reported that younger age, use of felbamate, and use of an opioid were predictive for pneumonia, but that use of rufinamide was protective. Other covariates, including clobazam dose, history of pneumonia, history of aspiration, history of dysphagia/GE-reflux/feeding tube placement, history of drooling/hypersecretion, or AEs of drooling/hypersecretion prior to pneumonia, somnolence-related AE prior to pneumonia, AE within HLT of upper respiratory infection prior to pneumonia, and AE within HLT lower respiratory infection prior to pneumonia were not predictive. Dr. Boehm notes that these findings were consistent with the Sponsor's analysis of AEs that found in the 14 days preceding the pneumonia, only approximately 7% of the pneumonia AEs (7/106) occurred in patients with a somnolence related AE and 1 (0.9%) occurred in a patient with a drooling/salivary hypersecretion AE. Patients with pneumonia-related AEs were likely to have had a seizure preceding the pneumonia, as 8 of the 10 pneumonia events in the controlled trials occurred in patients who experienced a seizure in the preceding 5 days. The sponsor also found that clobazam dose increases in the 7 days prior to the pneumonia-related event occurred in approximately 7% (7/106) of the pneumonia-related AEs.

Twenty-three postmarketing reports of pneumonia with clobazam were found by the Sponsor. As Dr. Boehm notes on p. 92 of his review, many of the reports identified concomitant factors putting patients at risk for pneumonia AEs including seizure disorders, neurological deficits, and swallowing problems. Other reports included AEs temporally related to clobazam and preceding the development of pneumonia including increased secretions and difficulty managing secretions in 4 cases or altered level of consciousness in 4 cases.

Dr. Boehm examined the information available for FDA approved drugs for LGS (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide) to examine pneumonia risk in LGS AED programs. Clonazepam and lamotrigine did not have separate AE data for LGS trials. In the felbamate LGS trial that included 31 felbamate and 27 placebo subjects, pneumonia did not meet the criteria (>1 subject) for inclusion in the AE table in the label. In the topiramate sNDA medical review (5/9/98), in LGS trial YL, 2/50 (4%) of topiramate subjects had SAEs of pneumonia. In the rufinamide NDA submission, in the RCT 2 rufinamide (2.7%, 2/74) and no placebo patients (0/64) had AEs of pneumonia, and in the RCT and open label extensions the pneumonia AE risk was 8.1% (11/135). Thus, similar to the findings in the clobazam studies, pneumonia AEs were observed in LGS patients in the topiramate and rufinamide trials.

Dr. Boehm has also conducted a literature search and has found no publications suggesting a link between benzodiazepine use, including clobazam, and increased risk of developing pneumonia.

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I agree with Dr. Boehm that although there was an increase in pneumonia-related AEs with clobazam compared to placebo in OV-1012, this finding is based on a small number of events. Dr. Boehm notes the pretrial medication histories of many patients that included episodes of aspiration and pneumonia, and circumstances such as feeding tubes that could increase the pneumonia risk. He notes that pneumonia AEs were also observed in LGS development programs of other AEDs, and that pneumonia was not observed in the clobazam patients in Phase 1 trials or the Legacy Psychiatry trials, and that the risk was less in the legacy epilepsy trial than in the LGS trials. There were a relatively small number of pneumonia postmarketing reports, and there was not supportive evidence of a link between clobazam and pneumonia in the literature. *I agree with Dr. Boehm that there is insufficient evidence to determine if there is a causal relationship between pneumonia and clobazam, although the data are also not sufficient to exclude the possibility that clobazam might increase pneumonia risk within the LGS population.*

Blood dyscrasias – Blood dyscrasias AEs were only identified in the Phase 2/3 trials. In those trials 18 clobazam patients experienced 1 or more blood dyscrasias (n=0 in OV-1002, n=4 in OV-1012, and n=15 in OV-1004). Of these 18 patients, 16 experienced low platelet counts, 1 had red blood cell count decrease, and 1 had a leucopenia AE. One patient (0803-7115) had a low platelet AE in trial OV-1012 and again in OV-1004. Three patients experienced one or more thrombocytopenia SAEs, but these were confounded by concomitant administration of other AEDs associated with thrombocytopenia including valproic acid, carbamazepine, or phenytoin. All of the patients with nonserious thrombocytopenia AEs were taking other AEDs associated with thrombocytopenia at the time of the event.

Serious Skin Reactions – There were no cases of serious skin reactions identified in the clinical trials safety databases. As noted above, there was an SAE of “Adverse Drug Reactions” that was a rash requiring hospitalization in Subject 0058-7032.

Drug-Induced Liver Injury – Dr. Boehm has summarized the sponsor’s findings with respect to potential for drug-induced liver injury, assessed by reviewing lab data results and liver-related AE risks. I agree with Dr. Boehm’s assessment that the outlier data from the Phase 1 trials and the data from the Phase 2/3 trials do not suggest an increased risk for liver-related lab test elevations for clobazam patients. In the Phase 1 trials and in the Phase 2/3 trials, there were no cases in which subjects had transaminase elevations $\geq 3X$ ULN in association with total bilirubin $\geq 1.5X$ ULN. There were no increases in transaminases in those studies $\geq 10X$ ULN.

In the Legacy Epilepsy trial, no subject had transaminase elevation $\geq 3X$ ULN or total bilirubin \geq ULN. No subjects in the US and Canadian Legacy Psychiatry trials had transaminase elevation $\geq 3x$ ULN. No placebo subjects (0/51), 1

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clobazam subject (1/109), and 1 diazepam subject (1/540) experienced total bilirubin \geq 2x ULN.

Dr. Boehm has also summarized the liver-related AE risks from clobazam trials. In Phase 1 trials 7 (2%, 7/349) clobazam subjects had a liver-related AE (6 transaminase elevated, 1 alanine aminotransferase elevated) compared to 2 comparator subjects (1.4%, 2/140) with liver-related AEs (1 placebo, 1 active control, both with transaminase elevated). In OV-1002, 1 placebo patient and 1 low dose clobazam patient experienced a liver-related AE, and in OV-1012, 2 high dose clobazam subjects experienced a liver related AE. These AEs in clobazam patients were hepatic enzyme increased, alanine aminotransferase and aspartate aminotransferase increased, and blood alkaline phosphatase increased. The AEs were considered mild and did not lead to discontinuation. In the open label extension OV-1004, 9 subjects had liver related AEs (elevated LFTs n=7, alkaline phosphate increased n=2), 1 of which was serious. For details of that case, please refer to Dr. Boehm's review. In brief, Subject 0017-728 was a 5 y.o. female with LGS who experienced a non-serious AE of hepatic enzyme increased on Day 478 and a serious AE of hepatic enzyme increased on Day 855. She was receiving clobazam 10 mg daily at the time of the first event and 15 mg daily at the time of the second event. Elevated ALT values (range 4.68-9.88X ULN) and AST values (2.00-5.48 X ULN) were noted on Days 478, 485, 660, 848, 869, and 898. Total bilirubin and alkaline phosphatase values were within normal limits throughout the trial. Study drug dose was reduced on Day 890 to a total daily dose (TDD) of 10 mg and on Day 898 to a TDD of 5 mg. The patient was hospitalized on Day 885 for further evaluation. Abdominal ultrasound showed evidence of cholelithiasis and small gall stones, but no irregularities in the liver. Liver biopsy showed mild hydropic changes of hepatocytes and minimal lymphocytic infiltrate in 1 portal triad; no definitive evidence of toxic hepatitis, viral inclusions, PAS+, diastase resistant granules seen by special stain was identified. Despite stopping clobazam on Day 912, transaminases declined but continued to be elevated on day 1024 (ALT 2.68X ULN, AST 1.75 X ULN). The subject did not have severe hypotension or congestive heart failure that would explain the event. Serology was weakly positive for CMV, and positive for EBV nuclear antigen antibody. The subject was immunized for Hepatitis A and B. Hepatitis C was non reactive, and Hepatitis D and E serologies were not done. A consultant gastroenterologist considered overfeeding and steatohepatitis as a possible etiology. The sponsor provided a publication describing hepatic failure with phenobarbital (a concomitant medication in this patient) and summarized 13 cases from the literature of hepatitis or hepatic necrosis with phenobarbital. This patient was also treated with azithromycin, ciprofloxacin, and topiramate that have liver injury information in their labels. This case cannot be clearly attributed to clobazam.

There were no liver-related AEs in the Legacy Epilepsy trial. Three liver-related AEs were identified from the Legacy Psychiatry trials. Subject 0001-0004 experienced elevated LFTs and jaundice and was hospitalized; liver biopsy was

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reported consistent with alcoholic cirrhosis (SAE mentioned above). Subject 001-0171 experienced AEs of liver function test abnormal and aspartate aminotransferase increased. AST at visit 1 was 32 U/L; LDH was 174 U/L; ALT not reported. At visit 2, AST was 86 U/L and LDH was 219 U/L. Total bilirubin was normal at both visits. There were no results following visit 2. Subject 001-0099 had an AE of liver disorder, with ALT of 25 U/L (ULN) at 24 on visit 2; total bilirubin was not reported.

Lundbeck identified 54 cases of potential liver injury in postmarketing reports. Dr. Boehm notes that there did not appear to be any strong cases suggesting that clobazam was the cause of any of the serious events, and that in the majority of these cases patients were taking concomitant medications recognized as potential hepatotoxins.

Dr. Boehm conducted a PubMed search and did not identify publications implicating clobazam as a cause of liver injury. Dr. Boehm notes that benzodiazepines are not commonly identified as hepatotoxins in the literature.

I agree with Dr. Boehm's conclusion that the evidence does not suggest that clobazam is associated with liver injury.

Cancer – Dr. Boehm reports that the Sponsor found no cancer AEs in the Phase 1 or Phase 2/3 controlled trials. In the open label extension OV-1004, there were 3 cancer AEs: benign breast neoplasm, skin papilloma, and osteochondroma (all benign). One subject from the Legacy Epilepsy trial had a cancer AE that was a low grade astrocytoma and underwent left temporal lobectomy.

Suicidality – Analysis of suicidality AE data were limited to trials that met the criteria established by FDA in the 2005 suicidality analyses (criteria included only those trials that were randomized, parallel-arm, placebo controlled). The trials included in the analysis were OV-1012 and several legacy psychiatry trials. There were no suicidality AEs in OV-1012. In the legacy Psychiatry trials, one clobazam subject discontinued following a suicide attempt and 2 clobazam subjects experienced suicidal ideation.

SUDEP – Dr. Boehm reports that the Sponsor felt that 3 deaths from OV-1004 (open label extension trial) could potentially be SUDEP. Two subjects were found dead in bed (one of whom had chronic lung disease). One subject with spastic quadriparesis and a swallowing disorder was found at home without pulse or respirations. There were no potential SUDEP cases in the legacy epilepsy trial.

DRESS – The sponsor searched for AEs related to internal organ involvement (i.e. hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) in association with any one of the following: fever, rash, or lymphadenopathy. One case (Subject 0017-

7005) from the clinical trials databases met the AE term (and none from postmarketing databases or medical literature). The details of the case can be found in Dr. Boehm's review. The subject discontinued because of an AE of rash that occurred on Day 11 and Day 13 (mild and severe, respectively). At the time the subject was receiving clobazam 5 mg twice daily. The rash was associated with a "palpable spleen tip" according to the event description, as well as granulocytopenia, elevated sedimentation rate, anemia, liver enzyme elevation (AST approximately 6x ULN and ALT approximately 10X ULN), and fever. Relevant medical history included upper respiratory infection, fever, and diarrhea. Study drug was prematurely discontinued on Day 17. The mild rash resolved on Day 28 and the severe rash resolved on Day 66. The patient was not hospitalized. Concomitant medications recorded during the time of the event included amoxicillin, paracetamol, diphenhydramine, and ibuprofen. AEDs administered during the study included topiramate, levetiracetam, and valproic acid. Of note, the subject had been on valproic acid and topamax for almost 2 years then stopped then upon starting clobazam. They were restarted on Day 7 of clobazam. The subject was taking Motrin for upper respiratory infection beginning on Day 2 of clobazam. Lundbeck reported that a medical review of the case concluded it was not a case of DRESS. Lundbeck noted that the patient did not experience eosinophilia or lymphadenopathy and felt that in the setting of an upper respiratory tract infection, otitis media, and fever, this event most likely represented an infectious process. Dr. Boehm does not believe that this is a clear case of DRESS, noting the lack of consensus in diagnostic criteria that complicates evaluation of such cases. Dr. Boehm finds no literature publications of DRESS/drug hypersensitivity syndrome implicating clobazam and cites a review stating that "hypersensitivity syndrome has not been described in patients taking benzodiazepines".

I agree that there is a lack of consensus in diagnostic criteria for DRESS. Alternate criteria to those proposed by the sponsor are provided by the RegiSCAR project as follows: hospitalization, reaction suspected to be drug related with acute skin rash, involvement of at least one internal organ, enlarged lymph nodes at two sites at least, abnormalities in blood count (lymphocytes above or below lab limits, eosinophils above the lab limits, or platelets below the lab limits), fever above 38°C. At least 3 of these criteria should be present for DRESS/HSS.² I do not believe that DRESS can be ruled out. However, the case is confounded by an infectious process and recent initiation or re-initiation of concomitant medications, including ibuprofen, valproic acid, and amoxicillin, associated with DRESS^{3, 4} that precludes attributing this case to clobazam. In

² European Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples. <http://regiscar.uni-freiburg.de/diseases/dress/index.html>

³ Ibuprofen has been associated with 2 cases of probable DRESS based on a search of MEDLINE (Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. Am J Med 2011; 1224:588-597). That publication also found a case of definite DRESS with sodium valproate/ethosixime and a case of probable DRESS with amoxicillin plus clavulanic acid.

⁴ In a review by Dr. Lourdes Villalba dated 5/11/09, valproic acid, amoxicillin, and ibuprofen were among the drugs with EB05 >2 for the Preferred Term "DRESS" in a data mining analysis of AERS as of 11/2008.

addition, there is a lack of other evidence in this database for DRESS, and there is no evidence in the literature that clobazam or other benzodiazepines are associated with DRESS. Therefore, *I agree with Dr. Boehm that there is nothing to warrant placement of DRESS in the labeling of clobazam at this time. I also agree that it would be appropriate to monitor postmarketing reports and the literature for DRESS cases with clobazam if this drug is approved.*

Somnolence-Related AEs – Dr. Boehm notes that somnolence-related AEs are very common in clobazam treated subjects. In response to the Division’s request, the Sponsor summarized the frequency of somnolence related events (somnolence, hypersomnia, sedation, lethargy, and depressed level of consciousness) when grouped together, as verbatim terms did not indicate an obvious reason for use of separate preferred terms. The risk of somnolence related events among placebo subjects was 22% and for clobazam subjects ranged from 28-44%, with an apparent dose response as shown below from Dr. Boehm’s review:

Somnolence-Related AEs from the Controlled Phase II/III LGS Trials

AE	OV-1002		OV-1012			
	Clobazam 0.25mg/kg N=32	Clobazam 1.0mg/kg N=32	Placebo N=59	Clobazam 0.25mg/kg N=58	Clobazam 0.5mg/kg N=62	Clobazam 1.0mg/kg N=59
A least 1 somnolence related AE	28% (9)	39% (14)	22% (13)	28% (16)	32% (20)	44% (26)

Thirteen of the 85 clobazam treated subjects with a somnolence related AE discontinued for that event. Dr. Boehm notes that the frequency of somnolence related AEs in the open label trial OV-1004 was 24%, suggesting tolerance to these events over time. As shown in Dr. Boehm’s review (p. 51), a survival curve for somnolence-related events indicates that the majority of these events occurred during the first 25 days of treatment, which corresponded to the titration phase of the controlled trials. Dr. Boehm also notes that few additional somnolence-related AEs were reported after approximately the first 100 days of treatment. Similarly, in both OV-1002 and OV1012, an evaluation of these events by trial week showed that somnolence-related events occurred with highest frequency during titration, peaking around weeks 3-7, and declining by week 12, suggesting (subjective) tolerance to these effects.

In OV-1002, somnolence-related events lasted a median of 20 days (range 3-49) in the low dose group compared to a median of 32 days (32-76 days) in the high dose group. In OV-1012, somnolence related events lasted a median of 26.5 days (range 1-91) in the low dose group, 37.5 days (range 5-104 days) for the middle dose group, and a median of 15 days (1-95 days) for the high dose group; somnolence related AEs lasted a median of 5.5 days (range 1-92 days) in the placebo group.

Investigation of predictors of somnolence-related AEs in controlled LGS trials suggested that the odds for somnolence-related AEs increase with increasing clobazam dose, Hispanic ethnicity, and for subjects at US investigation sites. For pooled controlled and open label data, the odds increased with concomitant use of anesthetics and opioids and decreased with concomitant use of rufinamide.

2.3.5 Common Adverse Events

In the Phase 1 trials, 73% of subjects exposed to clobazam experienced one or more treatment emergent AEs (TEAEs). The AEs reported for $\geq 5\%$ of clobazam-exposed subjects were somnolence (29%), headache (18%), constipation (16%), dizziness (16%), and insomnia (8%), dermatitis contact (6%), tremor (6%), anxiety (6%), and decreased appetite (5%). Dr. Boehm reports that there were no AEs in Phase 1 trials coded to the preferred terms aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, acute renal failure, acute liver failure, pancreatitis, pancytopenia, or rhabdomyolysis.

In the Phase 2/3 trials overall, 92% (277/300) of patients had one or more AEs. Those reported for at least 5% of clobazam trial subjects were somnolence (25%), upper respiratory infection (24%), pyrexia (19%), pneumonia (15%), lethargy (14%), nasopharyngitis (14%), constipation (14%), aggression (13%), fall (13%), otitis media (13%), insomnia (12%), urinary tract infection (11%), drooling (11%), sedation (10%), skin laceration (10%), and convulsion, viral infection, diarrhea, vomiting, contusion, irritability, ataxia, sinusitis, decreased appetite, influenza, fatigue, cough, gastroenteritis, and pharyngitis streptococcal (all less than 10%). There were no AEs in Phase 2/3 trials coded to the preferred terms aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, acute renal failure, acute liver failure, pancytopenia, or rhabdomyolysis. Two cases of pancreatitis were discussed under SAEs.

In the Phase 2/3 RCTs, Dr. Boehm notes there were small differences in overall AE risk when comparing low dose and high dose clobazam groups in OV-1002, and when comparing clobazam and placebo groups in OV-1012. In OV-1002, 84% (27/32) of low dose patients and 86% (31/36) of high dose patients experienced one or more AEs. In OV-1012, 68% (40/59) of placebo patients, 72% (42/58) of low dose, 89% (55/62) of medium dose, and 76% (45/59) of high dose clobazam patients experienced 1 or more AEs. A dose response was noted for somnolence and constipation with clobazam. AEs reported for $\geq 5\%$ of clobazam patients and more frequently than placebo in OV-1012 were vomiting, constipation, pyrexia, irritability, fatigue, upper respiratory tract infection, somnolence, lethargy, drooling, ataxia, sedation, aggression, insomnia, and cough.

In the Legacy Epilepsy trial 301, 86% (102/119) of clobazam subjects and 87% (101/116) of active control subjects experienced one or more TEAEs. Those that

occurred in at least 5% of clobazam subjects were irritability, somnolence, aggression, attention deficit/hyperactivity disorder, negativism, restlessness, impulsive behavior, depressed mood, vomiting, dizziness, headache, ataxia, drooling, rash, social avoidant behavior, and convulsion. Dr. Boehm also notes that 1 clobazam subject (0.8%, 1/119) and no active control subjects (0/116) had an AE of pneumonia.

AEs that occurred in at least 5% of clobazam subjects in the Controlled Legacy Psychiatry Trials by analysis group were somnolence, dizziness, headache, and syncope in the US and Canada; somnolence, fatigue, dizziness, and dry mouth in the rest of the world; and somnolence in the non-CRF trials. In the Uncontrolled Legacy Psychiatry CRF Trials, somnolence was the only AE that occurred in at least 10% of clobazam subjects, and in the uncontrolled, non-CRF trials, irritability, tension headache, asthenia, fatigue, memory impairment, tension, initial insomnia, dyspepsia, middle insomnia, and myalgia were reported in at least 10% of clobazam subjects. As discussed above, pneumonia was not reported as an AE for any patients in the Legacy Psychiatry trials.

2.3.6 Laboratory findings

Dr. Boehm outlines the protocols and reporting methods used for laboratory evaluations and notes the weaknesses in some of the studies. He notes that for Phase 1 trials, the Sponsor identified patients with potentially clinically significant (PCS) lab results associated with AEs, but did not provide shift tables or mean change from baseline analyses. For Phase 2/3 trials, the sponsor identified PCS lab results and provided shift tables, and mean change from baseline analyses, with hematology and chemistry samples collected at baseline, week 3 (end of titration), week 7, week 11 (end of taper for OV-1002), and week 15 (end of taper for OV1012,). I agree with Dr. Boehm's approach to focus on the controlled studies rather than the pooled Phase 2/3 studies. For the Legacy Epilepsy Trial 301, the Sponsor identified PCS lab result outliers and provided shift tables and mean change from baseline analysis. However, the laboratory data were required by protocol only for the screening visit, and post-screening labs were only collected in cases that were deemed necessary. Therefore, Dr. Boehm notes that the results for that study do not represent comparisons of randomized groups. Dr. Boehm notes that for the Legacy Psychiatry trials, the sponsor identified PCS lab result outliers, and provided shift tables and mean change from baseline analyses. However, he notes the limitations of these data, including the small number of subjects with lab data available for analysis, and for a given parameter, only a subset of subjects within an analysis group might have been tested as the same tests were not performed on each subject.

Hematology - In Phase 1 trials, 5.2% of clobazam subjects (18/349) had a PCS low hematocrit result, the lowest of which was 31%. For 7/18 the result was PCS at the end of the trial. Only 1 subject had a PCS low hemoglobin result at the last visit. No clobazam subjects in Phase 1 trials had a PCS low platelet result.

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In Phase 2/3 Controlled Trials, Dr. Boehm notes an excess of low hemoglobin/hematocrit PCS outliers among clobazam patients (9% and 22% for hemoglobin/hematocrit) compared to placebo (5% and 12% for hemoglobin/hematocrit) in OV-2012, although he cautions that the small samples sizes and number of events precludes firm conclusions. He also notes that for the PCS low hemoglobin/hematocrit values, the changes were very small (the lowest on treatment hemoglobin dropped to 7.9 g/dL from a baseline of 8.4 g/dL). Dr. Boehm notes that the PCS data did not support an increased risk of low platelets in clobazam patients in these trials. The shift table for hematologic results in these studies showed that the percentages of patients that shifted from high or normal at baseline to low for hematocrit and hemoglobin were similar for placebo and clobazam patients in OV-1012. Dr. Boehm shows that the mean changes from baseline to final visit for the hematologic tests in these trials were small and notes that they are of unknown clinical significance.

In the Legacy Epilepsy trials, for which lab values post-baseline were taken only when considered necessary, 3 (9.1%, 3/33) clobazam and 3 (7.9%, 3/38) active comparator subjects experienced PCS low hematocrit values. No tested subjects had a PCS low hemoglobin, WBC, or platelets. Dr. Boehm notes that there did not appear to be differences in risks for shifts from normal or high at baseline to low for hematocrit or hemoglobin when comparing clobazam and active treatment groups. One clobazam subject (2.9%, 1/34) and 2 active treatment subjects (5.3%, 2/38) experienced WBC shifts from high/normal at baseline to low during the trial. No patients experienced low platelet shifts. I agree with Dr. Boehm that there did not appear to be meaningful differences in mean changes from baseline to final when comparing clobazam and active treatment groups.

In the Legacy Psychiatry Trials, as Dr. Boehm noted, laboratory data are available for only a subset of subjects from these trials, limiting any conclusions about the effect of clobazam on hematologic parameters. PCS low hematocrit values were identified in 2.3% (3/118) of clobazam subjects compared to 5.6% (4/71) of diazepam subjects, and PCS low hemoglobin low values were identified in 1.6% (2/128) clobazam subjects and none of the diazepam subjects in controlled legacy psychiatry trials, US and Canada. Hemoglobin and hematocrit were not reported for the controlled legacy psychiatry trials, rest of world. In non-CRF trials, the results were similar for clobazam as for diazepam. Shifts from high/normal to low in US/Canada were slightly higher for clobazam compared to placebo for hemoglobin (6.3%, 8/128) vs 3.8% (2/52) and for hematocrit (14.8% (19/128) vs 13.5% (5/72), and for hemoglobin in the non-CRF trials (4.9%, 3/61 vs 0, respectively). The mean changes from baseline to final were small.

Chemistry – Evaluation of PCS chemistry results in Phase 1 studies showed 12 clobazam subjects and 1 placebo subject with PCS chemistry results. For the 12 clobazam subjects, 3 experienced PCS ALT and AST, and 1 experienced PCS

ALT. Two clobazam subjects experienced PCS creatinine and 2 experienced PCS triglyceride results. One clobazam subject experienced PCS results for calcium, BUN, Potassium, and urate. The placebo patient experienced PCS ALT results.

Evaluation of Phase 2/3 trials showed infrequent PCS chemistry results. Parameters with more than 1 clobazam subject with PCS values were ALT, AST, ALP, or Bilirubin high, Bicarbonate low, BUN high, Calcium low, and Sodium high and were reported in < 7%. Based on the results presented on p. 62 of Dr. Boehm's review, I agree that there does not appear to be strong evidence of differences in PCS results in comparing clobazam to placebo. For OV-1012, the risk for shifting from normal/low at baseline to high was similar for clobazam and placebo for ALT and ALP. For AST, a higher percentage of clobazam patients shifted higher (3.4% for placebo, 8.6% for clobazam low dose, 6.5% for clobazam middle dose, and 16.9% for clobazam high dose). Dr. Boehm also notes somewhat higher risks for shifts higher for calcium, sodium, and triglycerides. He also notes that in OV-1012, the mean changes from baseline to final were generally similar for clobazam and placebo, except for ALP and triglycerides where the mean change was positive among clobazam patients and negative among placebo patients.

Dr. Boehm reports that for the Legacy Epilepsy Trial 301, only 1 clobazam subject had a PCS chemistry result (ALP high), and that shift results and mean changes from baseline were generally similar for clobazam and placebo subjects. As previously noted, these data have limitations. In Legacy Psychiatry Trials the only chemistry parameters that had more than 1 clobazam subject with a PCS result were low glucose (2/88) and high BUN (2/100). In the Controlled non-CRF trials, parameters with more than 1 clobazam subject with a PCS result were low albumin (2/63) and low phosphate (2/61). No subjects from the remaining legacy psychiatry trials had a PCS chemistry result and Dr. Boehm reports that shift results and mean changes from baseline were generally similar for clobazam, placebo, and active comparator subjects, noting again the limitations in the results and their interpretation.

Urinalysis – Dr. Boehm reports that for the Phase 1 trials, for clobazam exposed subjects, mean changes (pH and specific gravity) and shifts to abnormal for urine parameters were small and unlikely of clinical significance. He reports that in Phase 2/3 trials, shifts from normal at baseline to abnormal for urine parameters were infrequent and he does not find meaningful differences when comparing clobazam and placebo subjects, nor does he find differences for clobazam and placebo subjects in comparing mean changes from baseline to final for pH and specific gravity in OV-1012. Dr. Boehm reports that data from the Legacy trials provided little useful information.

2.3.7 Vital Signs

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In the Phase 1 trials, the sponsor identified the clobazam exposed subjects who had one or more PCS vital sign changes and reported that there were 7 subjects (5 clobazam, 2 placebo) with one or more PCS vital sign results. During the QT trial OV-1022 which administered doses of 40 mg and 160 mg/day, 2 clobazam and 2 placebo subjects experienced high pulse rates (highest 168 bpm). All 4 were reported to have sinus tachycardia AEs; none experienced dizziness, hypotension, syncope, or loss of consciousness. The 2 clobazam subjects were in the 40 mg dose group and Dr. Boehm notes that neither was a CYP2C19 poor metabolizer. In trial OV-1018 (a bioavailability study of 20 mg clobazam with or without a high fat meal), 1 clobazam subject had PCS pulse rates (highest 145 bpm) and an AE of sinus tachycardia on study Day 14. The event resolved that day and the subject did not experience dizziness, hypotension, syncope, or loss of consciousness. In OV-1022 (single 20 mg dose), 1 subject (with a baseline BP of 109/67 mm Hg) experienced low systolic and diastolic BP results (systolic BPs of 67, 77, and 89 mm Hg and diastolic of 46 mm Hg) on a dose of 160 mg/day. The subject had AEs of hypotension and dizziness on the same day. The events resolved the next day. In OV-1017, 1 subject experienced a PCS high diastolic BP of 105 mm Hg on Day 14. He had an AE of blood pressure increased on Day 10 and the event resolved on Day 21.

In Phase 2/3 studies, Dr. Boehm reports that neither the PCS analysis nor mean change from baseline to final analysis appeared to demonstrate consistent clobazam related vital sign changes. *I agree with his assessment.*

2.3.8 Electrocardiograms

ECG data come from the formal QT trial OV 1-022 and from ECGs performed during controlled trial OV-1012. Dr. Boehm notes that the sponsor did not find evidence of QT prolongation related to clobazam or its metabolite N-CLB in OV-1022, and ECGs from OV-1012 did not suggest repolarization prolongation in patients treated with clobazam.

The thorough QT (TQT) study OV-1022 was reviewed by the FDA IRT in a 8/9/11 memo as summarized by Dr. Boehm. They reported that no significant QTc prolongation effect of clobazam (40 mg and 160 mg) was detected, and that the largest upper bounds of the 2 sided 90% CI for the mean difference post-dose between clobazam and placebo were below 10 ms, the threshold of concern, in a study in which sensitivity was demonstrated with moxifloxacin as the positive control. The suprathereapeutic dose (160 mg) produced mean Cmax values of clobazam and N-CLB that cover scenarios in which drug interactions could increase exposure to either parent or its metabolite. The IRT has recommended specific labeling language.

Dr. Boehm notes in the TQT study, the sponsor reported that no subjects who received clobazam had QTc interval > 480 ms or experienced changes from baseline in QTc interval greater than 60 ms, and that none of the subjects who received clobazam had clinically important changes in ECG morphology. The

sponsor found no PK/PD relationship between clobazam or N-CLB plasma concentrations and QTc prolongation.

In OV-1012, ECGs were collected at screening, baseline, week 5, week 7, and week 15. There were no outliers for QTcF > 480. QTcF increase from 30-60 ms was reported for 3.4% (2/58) placebo patients, and for 5.4% (3/56) clobazam low dose, 8.1% (5/62) of clobazam medium dose, and 9.1% (5/55) high dose patients. There were no outliers for QTc increase > 60 msec. The mean change from baseline results do not suggest a signal for QTc prolongation for clobazam compared to placebo.

2.3.9 Dose-Dependency for Adverse Events

Dose-response relationships for AEs were evaluated using 2 Phase 1 trials, Phase 2/3 controlled trials, and concentration-response analyses using population PK data. Note that the Phase 1 trials did not enroll pediatric patients.

In the Phase 1 trial OV-1038 24 healthy adults were titrated to 80 mg bid over a 44 day period. Three subjects discontinued for AEs (one for dizziness and somnolence while receiving 70 mg BID, one for somnolence while receiving 60 mg BID, and the third because of elevated transaminases while receiving 10 mg and 15 mg BID). Dr. Boehm notes that none of these subjects were CYP2C19 poor metabolizers. Dr. Boehm does not note a clear dose response for AE risks, and I agree. Contact dermatitis, constipation, dizziness, and somnolence were the only AEs reported by at least 3 subjects. The 4 somnolence AEs were reported at clobazam doses of 20 mg BID, 25 mg BID, 60 mg BID, and 70 mg BID.

In the TQT study OV-1022, clobazam was titrated to the final dose over a 28 day period. Ten clobazam subjects discontinued for AEs (3 in the 20 mg BID group, 7 in the 80 mg BID group) compared to 2 placebo and 1 moxifloxacin subjects. In the clobazam 20 mg BID group, 2 subjects discontinued for transaminase elevations and one for mental status changes. In the clobazam 80 mg BID group, 2 subjects discontinued for delirium and one subject each for each of the following AEs, somnolence; delirium and depressed mood; decreased libido, erectile dysfunction and insomnia; dysarthria and unsteady gait; and dizziness. Dr. Boehm has identified the AEs that occurred in at least 5% of clobazam subjects and that were twice as common in the 80 mg BID group compared to the 20 mg BID group. Of those, the AEs that occurred in > 10% in the suprathreshold dose group were somnolence (33% in the 160 mg group vs 13% in the 40 mg group), dizziness (31% in the 160 mg group vs 7% in the 40 mg group), dysarthria (16% in the 160 mg group vs 1% in the 40 mg group), and gait disturbance (13% in the 160 mg group vs 1% in the 40 mg group).

In both Phase 2/3 trials, as noted above under discontinuations, Dr. Boehm notes a suggestion of a dose response for discontinuations due to AEs, although there

was not a strong dose response relationship for any particular AE leading to discontinuation. In addition, I agree that there did not appear to be a clear dose response for overall AEs in these trials, although there is a potential dose response for somnolence and for constipation. In OV-1002 somnolence occurred in 13% of low dose and 19% of high dose subjects and in OV-1012, somnolence occurred in 12% of placebo subjects, 16% of low dose, 24% of medium dose, and 25% of high dose clobazam subjects. Somnolence-related events, discussed above, showed a dose-response when grouped together. In OV-1002, constipation occurred in 3% of low dose and 8% of high dose subjects and in OV-1012, constipation occurred in 0 placebo subjects, 2% of low dose, 2% of medium dose, and 10% of high dose subjects.

The sponsor examined a dose and concentration response for sedation-related AEs and found that dose as well as both clobazam and/or N-CLB concentrations positively correlated with the incidence of any sedation-related event during treatment. They found no covariates as explanatory variables including the presence of AEDs.

2.3.10 Time-Dependency for Adverse Events

Dr. Boehm has examined the incidence of treatment emergent AEs (that occurred in at least 10% of clobazam study subjects) by time in the Phase 2/3 clobazam trials. The incidence appears to be fairly constant over time.⁵ The prevalence of common AEs appears to increase for the intervals examined during the first 6 months of use.

2.3.11 Drug Interactions

The sponsor evaluated AEs looking for potential drug-demographic interactions (age, sex, race, and region) in the pooled Phase 2/3 trials (controlled and open label). Dr. Boehm notes the limitations in interpreting these analyses due to the lack of an untreated comparator group and the small number of subjects and AEs in the placebo-controlled study. As Dr. Boehm notes, it is not possible to determine if observed differences in risk are due to drug-demographic interactions or represent differences due to the demographic variable that would be observed in the absence of drug. In evaluating the age categories of 2-11 years, 12-16 years, and > 16 years (and not including 1 patient who was < 2 y.o.), pyrexia, otitis media, pneumonia, and upper respiratory tract infections decreased in frequency with increasing age, while drooling, urinary tract infections, and skin laceration increase with increasing age. I note that the Office of Clinical Pharmacology review cites a paper by Greenblatt et al (Br J Clin Pharmacol 1981; 12:631-636) that shows a prolonged elimination half-life in elderly vs young males (48 h vs 17 h, $p < 0.01$). Given the possibility of dose-related somnolence and constipation, it may be prudent to titrate more slowly in the elderly as it will take approximately 10 days to get to steady state based on

⁵ Although the incidence table on page 72 of Dr. Boehm's review shows an increase in some events (including somnolence) in the interval of Day 78-179, this interval is much longer than any of the other intervals that generally cover approximately 1-4 weeks.

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these data. When stratified by sex, urinary tract infections occurred more commonly in females and insomnia in males, with a 2x difference in each case. When stratified by race, Asians tended to have lower AE risks compared to White, and Other. Stratified by region the US tended to have the highest AE risks compared to Rest of World and India but the sponsor commented that these differences may represent cultural differences. I note that in the evaluation of region, 230 patients were from US, 53 were from India, and 230 were from Rest of World. *I agree with Dr. Boehm's comment that it cannot be determined from the available data whether demographic-related differences are due to the demographic variable alone.*

Drug-disease interactions were evaluated in the Phase 1 trial in patients with renal impairment and a Phase 1 trial in hepatic impairment that was published in the literature. In OV-1032, the renal impairment study, single 20 mg and multiple 20 mg doses (every day for 7 days) were given to healthy subjects and to patients with mild and moderate renal impairment. The sponsor noted that there were no deaths, SAEs, AEs resulting in withdrawal, and no clinically important physical exam, vital sign, laboratory, or ECG findings. All subjects experienced at least 1 AE. The Sponsor noted minor differences in clobazam and N-CLB exposure for healthy subjects compared to those with moderate renal impairment but does not recommend dose adjustment. I note that clobazam and N-CLB normally do not account for a significant fraction of the dose in the urine, except in CYP2C19 PMs in whom N-CLB represents approximately 62-74% of the total metabolic products in the urine (compared to 25-29% in EMs). In OV-1032 there was one genotypic PM, a patient with mild renal impairment, who did not phenotypically express the PM trait based on plasma concentrations of N-CLB, with a C_{max} of only approximately 1.5x that of the matched control on Day 11. Therefore, there is little experience in CYP2C19 patients with renal impairment.

In a published trial in patients with hepatic impairment (5 with mild-moderate cirrhosis and 4 with severe cirrhosis), a decrease in clobazam C_{max} of 32% was observed in patients with liver disease compared to healthy subjects, with no significant difference in C_{max} for N-CLB following a single dose of clobazam. The T_{max} for N-CLB was prolonged in liver disease. There was no difference in clobazam clearance. However, I note that the mean elimination half life of clobazam in patients with hepatic impairment was approximately 2x that of the half life in healthy volunteers. (b) (4)

However, the Division has requested from the Sponsor a comprehensive evaluation supporting that recommendation.

Drug-Drug Interactions were evaluated in Phase 1 trials and review of population PK modeling data, with respect to P450-mediated interactions. The sponsor did not find an effect of CYP3A inhibition or CYP3A induction on PK of clobazam or N-CLB that would require dosage adjustment. The Sponsor did not find an effect of CYP2C19 inhibition on clobazam or N-CLB concentrations that would

require a dose adjustment, although they note that because of the pharmacokinetics of the CYP2C19 inhibitor used and the slow formation of N-desmethyl clobazam, the effects on N-CLB may not predict the effects that might be observed at steady state. The Sponsor did not find meaningful changes in pharmacokinetics of substrates for CYP1A2 or CYP2C9 after administration of clobazam. They note that lower doses may be required for substrates of CYP2D6. They report findings consistent with mild induction of CYP3A4, but find no significant effect of clobazam or N-CLB on concentrations of valproic acid or lamotrigine.

CYP2C19 genotype – CYP2C19 PMs have 3 fold to 6-7 fold higher exposure to N-CLB compared to IM/EM or EM exposed individuals. Dr. Boehm notes that PMs treated with 40 mg/day had exposures similar to EMs dosed at 120 mg/day. There were few PMs in the clinical trials (6 from Phase 1 studies and 7 from Phase 2/3 studies). None of the Phase 1 PMs experienced an SAE and none discontinued for an AE. There were 3 PMs in Phase 1 trials exposed to supratherapeutic doses (120 mg n=1 and 160 mg n=2). The subject dosed at 120 mg/day to steady state had a moderate AE of delirium with N-CLB concentrations 13-15x higher than in IMs or EMs receiving 40 mg/day. The subjects dosed at 160 mg/day experienced dizziness and somnolence. The remaining PMs from Phase 1 studies received doses of 20 mg and 40 mg/day and had AEs similar to those seen in the rest of the Phase 1 population.

In the LGS trials, 1 subject from OV-1002 and 6 from OV-1012 were PMs. Three of the subjects were in the low dose group and 4 were in the high dose group during the RCT. None of these patients died and 3 experienced one or more SAEs including pneumonia (2 subjects), failure to thrive, influenza, respiratory distress, and seizures. One additional PM LGS subject experienced pneumonia that was not an SAE. None of the subjects discontinued for an AE and all except 1 continued into the open label study and had clobazam exposures of > 1 year. Dr. Boehm notes that the Sponsor did not use genotyping in the trials to inform dosing decisions. He thinks that Lundbeck's proposal that dose titration recommendations in labeling obviate the need for genotyping prior to treatment seems reasonable, although experience is limited. *I agree with Dr. Boehm.*

Dr. Boehm evaluated AEs in the data set with patients taking strong CYP2C19 inhibitors (10 patients with fluconazole, 1 with fluvoxamine, and none with ticlopidine). Dr. Boehm reports that most of these patients either experienced no AEs during the period of coadministration or experienced AEs that appeared to be related to the underlying condition (e.g. candidiasis, sepsis, dermatitis). He notes 3 cases suggestive of a possible interaction. One was a somnolence AE that led to discontinuation from the study; one was a non serious AE of somnolence that ended when fluconazole was stopped. The third case had sedation and floppiness requiring hospitalization; fluconazole was stopped, clobazam was temporarily held, lamotrigine dose was reduced, and the subject recovered and continued in the study. As the sponsor notes, the drug interaction

study between clobazam and the CYP2C19 inhibitor omeprazole may not have been predictive of the steady state situation. Dr. Boehm's findings suggest that there may be a clinically significant interaction. *I agree with Dr. Boehm's suggestion that the Division should consider labeling language to alert prescribers to potential for AEs related to concomitant use of clobazam with CYP2C19 inhibitors.*

2.3.12 Human Carcinogenicity

Cancer-related AEs were designated events of special interest by the Sponsor and are discussed in Dr. Boehm's review (section 7.3.4) and in this review on page 12. Please also refer to the discussion of postmarketing AEs.

2.3.13 Human Reproduction and Pregnancy Data

Dr. Boehm notes that the Sponsor proposes classification as Pregnancy class C as reproductive toxicity studies demonstrate adverse effects on fetal development but there are no data from adequate and well controlled trials in humans or reliable post-marketing data that low evaluation of effects on reproduction and fetal development. (b) (4)

(b) (4)
The Sponsor's proposed labeling states that Onfi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The Sponsor's proposed labeling includes information about enrollment in the North American Antiepileptic Drug (NAAED) Pregnancy Registry.

Dr. Boehm notes that the sponsor acknowledges that administration of clobazam immediately prior to or during childbirth can result in the "floppy baby syndrome", manifested by hypothermia, hypotonia, respiratory depress, and difficulty feeding. The Sponsor notes that infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence and subsequently withdrawal, during the postnatal period.

In the development program, there were no pregnancies in the LGS clinical trials or the Legacy Epilepsy trial 301. There were pregnancy exposures in the Legacy Psychiatry trials but the study reports provided no information about those events.

The sponsor identified 131 postmarketing case reports of pregnancy exposure, of which there were only 21 unique cases where clobazam was the only or the primary suspect drug identified by the reporter. Six of those were normal deliveries and 3 did not include information about outcome. Dr. Boehm has summarized the 12 remaining unique cases on p. 84 of his review. Three of these cases were spontaneous abortions. Several of the cases appear to be manifestations of "floppy baby syndrome" described above or of drug withdrawal, and three with congenital abnormalities (1 case each) of hypertrophic cardiomyopathy, bilateral talipes, and diaphragmatic hernia. Dr. Boehm has also summarized 7 additional case reports of clobazam exposure during pregnancy

from the 120 day Safety Update, 4 of which had concomitant exposure to confounding AEDs. Congenital malformations in these reports included 1 each of limb reduction defects; absent tooth enamel; absence of external auditory meatus, hyperechogenicity of the kidneys, and hearing impairment; ear malformation, open wound of internal structures of mouth, deafness, and speech disorder. There were 3 reports of infants with respiratory failure, low birth weight, and GERD. In some cases clobazam was said to have been discontinued at the beginning of pregnancy (although the exact time is not known) and in some cases taken beginning prior to and throughout pregnancy.⁶

Dr. Boehm has summarized the Sponsor's search of the medical literature for publications describing pregnancy exposures to clobazam. One report was that of an open-label uncontrolled study in 3 subjects who took clobazam throughout their pregnancies; 2 subjects had normal infants and 1 had a child with persistent pulmonary hypertension of the newborn and who later showed features of attention deficit disorder. The Sponsor identified 2 trials where clobazam was administered in the final trimester of pregnancy. In the trial by Baudat et al, a randomized, double blind, placebo controlled trial of clobazam 15 mg daily for anxiety in 17 women in their final trimester, 1 subject discontinued due to cesarean section for placenta previa. The other deliveries were without complication and anomalies were not observed. The second trial was performed to investigate maternal-fetal transfer of clobazam after administration as an anxiolytic at a single oral dose of 20 mg. Twenty-one newborns were monitored at birth and on Day 5 for clinical signs and were compared to a control group of 9 infants born to mothers without administration of drug. Drug concentration in mother and fetus were near similar levels. One infant exhibited difficulty breathing, but there was no detectable clobazam level in an umbilical sample 40 minutes following drug administration or on Day 5 in that infant. All other clinical measurements in all infants showed no statistical difference between test and control groups.

There were 2 publications describing 3 pregnancies with multiple exposures including clobazam. One patient received valproate and clobazam and delivered a 3210g infant, Apgar score of 6-9, with hypothermia, cyanosis, and trembling. One case was a patient who received lamotrigine and clobazam throughout her pregnancy and had a premature infant (35 weeks, weight 2580 g) with Apgar scores of 4/8/10, no malformations, but transient respiratory distress and thrombocytopenia. A third case was a patient who received vigabatrin, carbamazepine, and clobazam during her pregnancy and had a full term infant with no malformations or disorders. A third publication (Robert et al).reported no malformations with use of clobazam either with valproic acid (2 patients) or phenobarbitone and carbamazepine (1 patient) during the first trimester. There was 1 publication reporting a withdrawal syndrome in an infant exposed to

⁶ According to Dr. Boehm's review, the case of hypertrophic cardiomyopathy occurred with an exposure of 2-3 doses at week 36. This is unlikely related to clobazam use.

clobazam in utero, with time to onset of withdrawal 24-48 hours that lasted up to 2 weeks.

Clobazam and N-CLB are reportedly transferred into breast milk.

There have been no adequate and well-controlled studies that could evaluate risk associated with gestational exposure to clobazam. The case reports similarly do not provide enough information to support inclusion in the labeling of information regarding birth defects.

2.3.14 Pediatrics and Assessment of Effects on Growth

I agree with Dr. Boehm that the data regarding height or weight changes are not of value in determining if clobazam has an effect on growth. The height data were not collected uniformly or using precise methodology, and height measurements were only required at Day -1. The short duration of the clinical trials and questions about the validity of using population based data for growth comparison preclude conclusions about clobazam's effect on growth.

2.3.15 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose cases have been reported for clobazam, including 4 post-marketing cases of fatal overdose. For the non-fatal overdose cases, the AEs reported included coma, somnolence/sedation, gait disturbance, nausea, asthenia, ataxia, bradycardia, decreased appetite, fatigue, hyperkinesia, hypotonia, and vertigo. One nonfatal case included a multidrug (clobazam, phenytoin) and alcohol ingestion treated in the ICU with flumazenil, activated charcoal, and hemodialysis.

With respect to abuse potential, the sponsor has submitted no formal clinical abuse liability studies. Clobazam has been classified as Schedule IV by the Drug Enforcement Administration since 1984. A review (dated 8/2/11) by the Office of Surveillance and Epidemiology (OSE) of cases of misuse, abuse, and overdose with clobazam in the AERS and WHO Vigibase databases did not provide strong evidence of abuse, misuse, or overdose.

Withdrawal-related AEs were evaluated in Phase 1 trials where clobazam was abruptly stopped without tapering and in Phase 2/3 LGS trials where subjects who discontinued were tapered off clobazam. In the Phase 1 trials, 68/207 enrolled subjects experienced 193 withdrawal-related AEs, most of which were reported within the first 7 days. Dr. Boehm notes that the risk seems to increase with clobazam dose at the time of discontinuation from the 4 Phase 1 trials included in this analysis. However, Dr. Boehm notes that an objective assessment of withdrawal using the CIWA-B questionnaire did not find a clear relationship between withdrawal risk and dose in OV-1022 or in Phase 1 trials OV-1023 (single daily dosing on Day 1 and Days 4-19) and OV-1038 (given either as BID dosing on Days 1-44 followed by single daily dose for next 15 days or as dose escalation Days 1-40, BID for 11 days, and then single dose for next

15 days). The most commonly reported withdrawal AEs were headache, insomnia, anxiety, tremor, palpitations, hyperhidrosis, irritability, decreased appetite, diarrhea, and visual impairment/vision blurred. Through the 120 day safety update, in the Phase 2/3 LGS trials, 93 subjects discontinued clobazam and no withdrawal-related AEs were reported.

2.3.16 Postmarket Experience

Clobazam is marketed in over 80 countries by Sanofi-Aventis and it was first approved in Australia over 40 years ago. Dr. Boehm notes that the [REDACTED] (b) (4)

[REDACTED] The AE reports date back to 3/11/76. Through 11/30/10 there were 2,043 postmarketing reports that described 4,335 AEs in patients treated with clobazam. The most commonly reported indication for use recorded in the reports was seizures, and Dr. Boehm notes that other commonly reported indications were therapeutic procedures and supportive care NEC, and anxiety disorders and symptoms. The mean age for the reports was 34.7 years (median 33 years, range < 1 day to 93 years); most reports were for patients ≥16 years to < 65 years (884), followed by 2 years to ≤12 years (n=222), and ≥ 65 to < 75 years (109) and there were approximately 80 reports in each of the age groups of < 2y.o., ≥12 y.o., and > 75 y.o.

The most commonly reported AE SOC were Nervous system disorders (25.3%), Psychiatric disorders (14.6%), General disorders and administrative site conditions (13.4%), and these also were the most commonly reported AE SOC for pediatric patients alone. The most commonly reported AEs overall were somnolence, convulsion, drug exposure during pregnancy, and drug ineffective, and in the pediatric group these were also the most common, along with drug interaction and aggression. There were 74 postmarketing reports with an outcome of death, of which many did not have a specific cause identified. Known cause of death in which more than 1 case was reported were overdose (n=11), drug exposure during pregnancy (n=9), pneumonia (n=5), liver failure (n=5), multiorgan failure (n=4), cardiac condition (n=4), 3 each of cerebrovascular disease, respiratory depression, restless/anxious, seizure, and suicide, and 2 each of myocardial infarction and sudden death.

Dr. Boehm has reviewed postmarket event reports of interest. Please refer to his review for details. There were 23 reports of pneumonia or pneumonitis and Dr. Boehm notes that many reports identified concomitant factors that put patients at increased risk; in 4 cases the event occurred after patients experienced increased secretions after starting clobazam and in another 4 pneumonia occurred in patients that developed altered level of consciousness on clobazam. There were 66 cases that included blood dyscrasia AE terms, including thrombocytopenia and platelet count decreased, pancytopenia, aplastic anemia, agranulocytosis, and bone marrow failure. I agree with Dr. Boehm's assessment that confounding factors such as concomitant medications, comorbid disease, lack of temporal association, or lack of detail do not allow for determination of a

causal relationship with clobazam. Postmarketing reports of serious skin reactions included SJS and TEN. The cases generally had confounding factors including multiple medications that have also reportedly caused SJS/TEN, negative rechallenge, a temporal relationship inconsistent with clobazam, or in some cases not well documented. There is not enough information in some cases to rule out a role for clobazam, and I agree with the placement of this information in postmarketing reports. Dr. Boehm has reviewed the sponsor's submission of postmarketing drug induced liver injury reports. Dr. Boehm reviewed a subset of cases of potentially concerning liver injuries including hepatitis and I agree with him that none of the reports clearly suggested that clobazam was causally related to the event (none described positive rechallenge, all had concomitant medications some of which have been associated with hepatotoxicity, in some cases clobazam had been used for years prior to the event, some documented resolution with continued clobazam treatment, some had documented negative rechallenges, and some had too few details). Please refer to his review for details. There were 11 postmarketing reports identified by the Sponsor as malignancies, although Dr. Boehm notes that one of those cases was not a malignancy. As for the other postmarketing reports, they time course was implausible, the report did not provide adequate information, multiple medications were involved, or the report identified an adequate alternative etiology so that causality could not be attributed to clobazam. The Sponsor reported 1 case of SUDEP in a patient taking carbamazepine and clobazam. Dr. Boehm does not believe that all postmarketing reports of sudden deaths were assessed to identify potential cases of SUDEP. The Sponsor identified 7 potential reports of DRESS, and I agree that in all cases, patients were treated with concomitant medications some of which have been associated with DRESS, one noted a negative rechallenge with clobazam, others noted resolution with continued clobazam treatment, and one report identified an alternative etiology for the event (strontium).

2.3.17 Summary of Significant Safety Concerns:

Dr. Boehm has not identified safety issues that would preclude the approval of clobazam. I *agree with his assessment*. Dr. Boehm has recommended some modifications to the proposed label.

2.3.18 Postmarketing Risk Management Plan

Lundbeck submitted a proposed Risk evaluation and Mitigation Strategy (REMS) with the original submission that includes a medication guide and a Timetable for Submission of Assessments. On April 25, 2011 the Agency notified the Sponsor that we do not believe that it is necessary for the Medication Guide to be part of a REMS, and requested an email to acknowledge the Sponsor's agreement of "no REMS" for this NDA. That agreement was sent by the Sponsor on April 27, 2011.

2.3.19 Conclusions

Safety Team Leader Memo
NDA 202067

Dr. Boehm has reviewed the safety issues associated with clobazam use. There are no safety issues that would preclude approval. I agree with his assessment. He has recommended some modifications to the labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY U YASUDA
08/31/2011

CLINICAL SAFETY REVIEW

Application Type	NDA
Application Number(s)	202-067
Priority or Standard	Standard
Submit Date(s)	12/23/10
Received Date(s)	12/31/10
PDUFA Goal Date	10/23/11
Division / Office	DNP/ODE 1
Reviewer Name(s)	Gerard Boehm, MD, MPH
Review Completion Date	8/23/11
Established Name	Clobazam
(Proposed) Trade Name	ONFI
Therapeutic Class	Anticonvulsant
Applicant	Lundbeck
Formulation(s)	5mg, 10mg, 20mg Tablet
Dosing Regimen	≤30kg 5mg daily titrated to 10-20mg (divided doses, twice daily) >30kg 10mg daily titrated to 20-40mg (divided doses, twice daily)
Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age or older
Intended Population(s)	Lennox-Gastaut patients

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7 Review of Safety

Safety Summary

This review considers the safety data for clobazam as presented in Lundbeck's NDA 202-067. Lundbeck seeks FDA approval for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients at least 2 years old. Clobazam is an orally administered 1,5-benzodiazepine. The exact mechanism of action for clobazam is not known but the presumed mechanism is as a positive allosteric modulator at gamma containing GABA(A) receptors.

Clobazam is approved in over 80 countries for the treatment of anxiety disorders and seizures. Clobazam was first approved in Australia over 40 years ago and since 1998, there have been an estimated [REDACTED] ^{(b) (4)} person-years of use. Sanofi-Aventis is the marketing authorization holder for clobazam in the majority of worldwide markets. Lundbeck (formerly Ovation) acquired the US, Canadian, and Mexican marketing rights from Sanofi-Aventis in 2004.

There are 5 FDA approved medications for LGS (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide), but none of these treatments are completely efficacious in all patients. In addition, toxicities (hepatic, hematologic, dermatologic, etc.) of the approved LGS treatments can limit their use. For these reasons, additional LGS treatments are needed.

The clobazam NDA submission summarizes safety data from 56 clinical trials including 2,236 exposed subjects. This exposure total includes safety data from trials conducted by Lundbeck (8 Phase I trials, 3 Phase II/III LGS trials, 633 exposed subjects) as well as safety data from 45 trials conducted by previous sponsors. The trials conducted by previous sponsors are referred to as Legacy trials. The Legacy trials were conducted from the 1970s through the 1990s, include data from non-US clinical development programs, and in many cases lack source data. Lundbeck submitted these legacy trials data "for completeness".

The Lundbeck trials included 8 Phase I trials and 3 Phase II/III LGS trials. The 8 Phase I trials were conducted in healthy volunteers (n=7) and in patients with renal impairment (n=1). The 3 Phase II/III LGS trials included 2 RCTs (OV-1002, OV-10012) and one open label extension trial (OV-1004). OV-1002 was a randomized, double-blind, low dose (0.25mg/kg) v. high dose (1.0mg/kg) adjunctive treatment trial in patients aged 2-30 years with LGS. The trial included a 4 week baseline phase followed by a 3 week titration phase and a 4 week maintenance phase. OV-1012 was a double-blind, adjunctive treatment trial that randomized patients with LGS to placebo, or one of 3 clobazam doses (0.25mg/kg, 0.5mg/kg, or 1.0mg/kg). OV-1012 included a 4 week baseline phase followed by a 3 week titration phase and a 12 week maintenance phase.

At the end of trials OV-1002 and OV-1012, patients were either tapered off clobazam, or enrolled to continue in the open label extension trial OV-1004.

The Legacy trials included a trial in children with epilepsy (301), and 44 trials in patients with psychiatric diseases including anxiety and neuroses.

Considering only the clinical trials conducted by Lundbeck, the exposure in the clobazam NDA does not meet the ICH guideline recommendations. Lundbeck reported that in their development program trials, 633 subjects were exposed to clobazam. Of this group, 253 subjects were exposed to clobazam for at least 6 months, and 197 for at least 12 months. Inclusion of the 1,603 subjects in Legacy trials in exposure estimates increases the total number of unique patients exposed to clobazam, but since many of these trials lack dose, start date, and stop date data, they cannot provide complete information about exposure by duration or by dose and duration.

The relatively small Lundbeck clinical trials exposure is augmented by the Legacy trials, which have the limitations mentioned above, and post marketing experience with clobazam. As noted above, clobazam has been approved in over 80 countries and was first approved over 40 years ago. Lundbeck summarized available post marketing safety data for clobazam. Specifically, Lundbeck summarized spontaneous post marketing adverse event reports and published reports of adverse events that mentioned clobazam.

Aside from the exposure limitations noted above and known by the Division prior to Lundbeck's filing of the NDA, I identified no significant deficiencies in the NDA safety submission. Lundbeck submitted all necessary summaries and supporting data. There were no notable inconsistencies between the data sources. The routine clinical safety testing in the clobazam LGS trials seemed appropriate. The clobazam NDA included instances of coding inadequacies, but these were addressed by Lundbeck in their analyses and therefore are not expected to hinder our understanding of the safety profile of clobazam.

Lundbeck reported 9 deaths in clobazam exposed subjects. No deaths occurred in clobazam subjects in Lundbeck's Phase I trials, Phase II/III LGS RCTs, or the Legacy trials. All 9 deaths in clobazam exposed subjects came from Lundbeck's open label LGS extension trial. Five deaths had respiratory etiologies (pneumonia, n=4; respiratory failure). These patients had underlying medical conditions (neurological disabilities, documented aspiration, gastroesophageal reflux, feeding tubes, etc.) that put them at high risk of respiratory disorders and infections. Three of the pneumonia death narratives mentioned aspiration (2 followed seizures). The reported causes of the remaining 3 deaths were epilepsy, natural causes with underlying seizure disorder, and unknown etiology.

Thirty-four percent (103/300) of subjects in the Phase II/III LGS trials experienced one or more serious adverse events (SAEs). The System Organ Class for which most subjects had an SAE was Infections and Infestations (17.3%, n=52). The most commonly reported SAEs were Pneumonia (8.7%, n=26), Convulsion (7%, n=21), pneumonia aspiration (3.3%, n=10), lobar pneumonia (2.3%, n=7), status epilepticus (2%, n=6), and urinary tract infection (2%, n=6). No subjects experienced SAEs of aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic Epidermal Necrolysis, acute renal failure, acute liver failure, rhabdomyolysis, angioedema, or anaphylaxis. In Lundbeck's RCT OV-1002, 3.1% (1/32) of the clobazam low dose patients experienced an SAE compared to 8.3% (3/36) of the high dose patients. In RCT OV-1012, 3.4%, (2/59) of subjects in the placebo group experienced an SAE compared to 5.2% (3/58) in the low dose clobazam group, 9.7% (6/62) in the medium dose clobazam group, and 8.5% (5/59) in the high dose clobazam group. In OV-1012, pneumonia SAEs were not reported for any placebo patients and were reported for 3.4% (n=2) of the low dose patients, 3.2% (n=2) of the medium dose patients and 1.7% (n=1) of the high dose patients. Pneumonia SAEs were not reported in OV-1002. No other SAE was reported for more than 3 patients in the LGS RCTs.

In all three clobazam phase II/III LGS trials, 16% (46/300) of patients had one or more AEs that led to discontinuation. The AEs leading to discontinuation of more than one patient were somnolence (n=7), aggression (n=6), lethargy (n=5), ataxia (n=4), pneumonia (n=3), death (n=2), fatigue (n=2), insomnia (n=2), restlessness (n=2), and urinary incontinence (n=2). In the 2 controlled phase II/III clobazam LGS trials, overall discontinuations due to AEs suggested a dose response. In trial OV-1002, 10% (3/32) of low dose clobazam patients discontinued for AEs compared to 11% (4/36) of high dose patients. In trial OV-1012, 3% (2/59) of placebo patients discontinued for AEs compared to 7% (4/58) of clobazam low dose, 13% (8/62) of clobazam medium dose and 22% (13/59) of clobazam high dose patients. The small number of specific AEs leading to discontinuation events did not provide robust evidence of dose response.

AEs that occurred more frequently among clobazam LGS subjects and in some cases that exhibited evidence of a dose response relationship included somnolence, constipation, lethargy, sedation, aggression, irritability, pyrexia, drooling, insomnia, pneumonia, and cough.

In accordance with the known effects of benzodiazepines, somnolence-related AEs were among the most common AEs reported during clobazam clinical trials. When all somnolence-related AEs (somnolence, sedation, lethargy, hypersomnia, and depressed level of consciousness) were considered together, in trial OV-1012, these events occurred in 22% (13/59) of placebo patients and 35% (62/179) of clobazam patients. Furthermore, the risk for somnolence-related AEs demonstrated dose response. The risk for a somnolence-related event was highest during the first 25 days of treatment. For 219 somnolence-related AEs in LGS clinical trials, investigators reported that 157 resolved. Somnolence-related AEs appeared to be tolerated given that only 15%

(13/85) of clobazam treated LGS patients with a somnolence-related AE discontinued from the trial for that event.

Pneumonia AEs occurred commonly in the LGS studies. Of the 9 clobazam clinical trial deaths, 4 were in patients who had pneumonia. As noted above, pneumonia was the most commonly reported SAE in LGS patients. Lundbeck performed analyses that assessed the risk for all pneumonia AEs. In trial OV-1002, there were 2 non-serious pneumonia-related events, both in patients treated with high dose clobazam. In OV-1012, there were 8 pneumonia AEs (4.5%, 8/179) in patients taking clobazam (all SAEs, 2 low dose, 2 medium dose, and 4 high dose). In that same trial, 1 placebo patient experienced a pneumonia-related SAE (1.7%, 1/59). In trial OV-1004, the open label extension trial, 46 patients experienced one or more pneumonia-related AEs (15%, 46/300).

The pneumonia risk was higher in the LGS population than in other clobazam treated populations. No pneumonia-related AEs were reported during Phase I Lundbeck trials or the Legacy Psychiatry trials, and one pneumonia-related AE was reported during the Legacy epilepsy trial.

In response to the Division's request, Lundbeck provided additional analyses of the pneumonia-related AEs in LGS patients. Lundbeck reported that the highest risk for a pneumonia AE was in the first 500 days of treatment. Through logistic regression analyses, Lundbeck found that younger age, use of Felbamate, and use of an opioid were predictive for a pneumonia-related AE but not sex, ethnicity, race, region of trial site, treatment (clobazam low, medium, or high dose), or other considered factors. Lundbeck also found that somnolence related AEs, drooling/salivary hypersecretion AEs, and clobazam dose increases did not commonly precede pneumonia-related AEs, but that seizures frequently preceded pneumonia-related AEs in the RCTs.

Available data for other LGS approved AEDs suggest that pneumonia can occur commonly in LGS patients. In a LGS trial, 4% (2/50) of topiramate subjects had SAEs of pneumonia. In another LGS RCT, 2 rufinamide (3%, 2/74) and no placebo patients (0/64) had AEs of pneumonia, and 8.1% (11/135) of rufinamide treated patients in the RCT and in the open label extension, had a pneumonia AE.

Although pneumonia occurred commonly in LGS patients in the clobazam development program, there is insufficient evidence to determine if there is a causal relationship with clobazam. While there was an increase in pneumonia related AEs with clobazam compared to placebo in the only placebo controlled trial, this finding is based on a relatively small number of events and in a population at increased risk for pneumonia. Additional analyses did not appear to provide convincing supportive evidence an association between pneumonia and clobazam. In addition to the available clinical trial data, Lundbeck found relatively few post marketing reports of pneumonia, and in many of these cases the patients had underlying risk factors for pneumonia. A PubMed

search did not find publications suggesting a relationship between clobazam and pneumonia or benzodiazepines and pneumonia.



Biotransformation of clobazam's active metabolite, N-CLB, is mediated by CYP2C19. CYP2C19 can have genotypic polymorphisms that result in phenotypic poor metabolizers (PMs). Approximately 5% of the Caucasian population and 15% of the Asian population are CYP2C19 PMs. Lundbeck noted that PMs can have estimated 5-fold higher exposure to N-CLB compared to IM/EM or EM individuals. Lundbeck reported that PMs treated with 40mg/day (labeling recommended dose) had exposures similar to EMs dosed at 120mg to 160mg/day. Lundbeck performed CYP2C19 genotyping in 7 of their clinical trials. A total of 13 PM identified individuals were exposed to clobazam in Lundbeck's studies. None of the 6 Phase I trial identified PMs with clobazam exposure had an SAE. One subject in the Phase I trial OV-1038 dosed at 120 mg/day to steady state had a moderate AE of delirium. N-CLB concentrations were approximately 13 to 15-fold higher in this subject compared with IMs or EMs receiving 40 mg/day (labeling recommended dose). Of the 7 identified PMs in the Phase II/III trials, 3 experienced one or more SAEs. These SAEs included pneumonia (2 subjects), failure to thrive, influenza, respiratory distress, and seizures. Despite differences in exposure, Lundbeck feels that by recommending dose titration to effect obviates the need to genotype patients for CYP2C19 polymorphisms. Lundbeck's plan seems reasonable, although there are limited safety data in PMs to support this approach.

Lab data, vital sign data and ECG data collected during the clinical trials did not find convincing evidence of clobazam-related deleterious effects. A formal QT study did not find evidence of QT prolongation in subjects exposed to clobazam.

Clobazam will have a Medication Guide because of the Suicidality warning required by the Division for all antiepileptic medications.

Problem List/Recommendations

There are no safety issues precluding the approval of clobazam.

Lundbeck should incorporate the labeling language requested by the Division.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

In their ISS, Lundbeck summarized safety data from 56 clobazam clinical trials. Lundbeck divided the safety data from these trials into the following categories: Phase I trials (n=8), Phase II/III Lennox Gastaut (LGS) trials (n=3), Legacy Epilepsy Trial 301 (from the previous sponsor), and Legacy Psychiatric trials (from the previous sponsor, n=44). Lundbeck noted that the Legacy trials date back in some cases to the 1970s, include data from non-US clinical development programs, and in many cases lack source data (Case Report Forms, CRFs). Lundbeck submitted these Legacy trials data “for completeness” (ISS, p.25).

Lundbeck Phase I Trials

Lundbeck summarized data from their 8 Phase I clobazam trials. These trials exposed 333 unique subjects to clobazam. Seven trials enrolled healthy adults and one enrolled subjects with renal impairment. The following table briefly summarizes these studies.

Summary of Lundbeck’s Phase I Clobazam Trials

Trial	Type	Number of Clobazam Subjects	Clobazam administration
OV-1016	Bioequivalence	40	Single dose day 1 and day 14
OV-1017	Bioavailability	18	Single dose day 1 (tablet or solution) and day 14 (solution or tablet)
OV-1018	Bioavailability	48	Single dose day 1 and day 14 (with/without food)
OV-1021	PK	36	Single dose day 1, day 22 (with ketoconazole or omeprazole)
OV-1022	QT	140	Every 12 hours days 1-28, morning dose day 29
OV-1023	PK	18	Single dose day 1, single dose days 4-19 (with drug cocktail day 1, day 19)
OV-1032	PK	25	Single dose day 1, and days 5-11
OV-1038	PK	24	Group 1 BID dosing, dose escalation period 1 (days 1- 44), single dose for next 15 days. Group 2 BID dosing, dose escalation (days 1-40), BID for 11 days, single dose for next 15 days

From the study reports for OV-1016, OV-1017, OV-1018, OV-1021, OV-1022, OV-1023, OV-1032, and OV-1038

Lundbeck also noted that there were 14 additional Phase I trials that were conducted by the previous sponsor and are not included above or reviewed in the body of the ISS. Lundbeck reviewed the study reports and noted that these trials reported no deaths,

SAEs, or AEs of special interest and that the most commonly reported AE was somnolence (ISS, p.23).

Lundbeck Phase II/III LGS Trials

In the NDA presentation, Lundbeck included safety data from 3 phase II/III trials. Two were randomized, controlled, double blind, trials (OV-1002 low vs. high dose, OV-1012 placebo and 3 clobazam doses). The third trial (OV-1004) is the ongoing open label extension trial.

OV-1002 was a randomized, double-blind, low dose (.25mg/kg) v. high dose (1.0mg/kg) adjunctive treatment trial in patients aged 2-30 years with LGS. The trial included a 4 week baseline phase followed by a 3 week titration phase and a 4 week maintenance phase. At the end of the trial, patients were either tapered off clobazam, or enrolled to continue in the open label extension trial (OV-1004).

OV-1012 was a double-blind, adjunctive treatment trial that randomized patients with LGS to placebo, or one of 3 clobazam doses (0.25mg/kg, 0.5mg/kg, or 1.0mg/kg). This trial included a 4 week baseline phase followed by a 3 week titration phase and a 12 week maintenance phase. At the end of the trial, patients were either tapered off clobazam or enrolled to continue in the open label extension trial (OV-1004).

OV-1004 is the ongoing open label extension that enrolled patients from OV-1002 and OV-1012. Subjects were allowed to enroll in OV-1004 if in the preceding trial they did not have a serious or severe AE that the investigator felt was due to clobazam. For subjects from OV-1012, clobazam was started at 0.5mg/kg (not to exceed 40mg/day) and the maximum target dose is 2.0mg/kg (up to 80mg/day). For subjects from OV-1002 who enrolled in OV-1004, an unblinded physician determined whether to maintain the clobazam dose that the patient was taking at the end of OV-1002, or to adjust that dose.

Legacy Epilepsy Trial 301

301 was a randomized, double-blinded, active controlled monotherapy trial in children (6 months -17 years) with partial epilepsies or generalized tonic-clonic seizures. This trial was 1 year in duration and was conducted in the early 1990s in Canada. One arm included subjects with newly diagnosed epilepsy and no previous AED treatment; these subjects were randomized to receive clobazam or carbamazepine. The other 2 trial arms included subjects who failed prior AED treatment for either efficacy or safety reasons. The second arm enrolled subjects who failed prior carbamazepine treatment; these subjects were randomized to receive either clobazam or phenytoin. Subjects who failed treatment with an AED other than carbamazepine were enrolled in the third arm and were randomized to receive either clobazam or carbamazepine. Trial medication was titrated over 1 to 3 weeks to a daily target dose of clobazam 0.5mg/kg, carbamazepine 10 mg/kg, or phenytoin 5 mg/kg. For those subjects who were receiving an AED at trial entry, the AED was discontinued during the initial 3-week titration period

so that all subjects were receiving monotherapy by the end of 3 weeks. Investigators were allowed to increase or decrease trial medication for an individual subject according to clinical response.

Legacy Psychiatry trials

Lundbeck reported on 44 legacy psychiatry trials (35 controlled, 9 uncontrolled). These trials were conducted over 40 years ago and did not conform to the prospective data collection standards of today. Thirty-one trials have CRFs and 13 do not. Data from these trials cannot be verified due to lack of access to trial sites/personnel. When these trials were conducted, there was no regulatory definition of SAEs and these events were not prospectively reported. Lundbeck noted that these trials were mainly for the indications of anxiety and neuroses, and the majority of trials were ≤ 6 weeks. These trials examined clobazam dose ranges from 10mg to 120mg/day.

Data Cutoff Dates

Except for the ongoing open label trial OV-1004, at the time of the NDA submission the clobazam clinical trials were finished and the safety data was complete. For trial OV-1004, Lundbeck identified 7/1/10 as the cutoff date in the NDA for the majority of safety data (exposure, adverse events, lab data etc.). Lundbeck did provide additional information in the NDA about deaths through 11/30/10. In their 120 day safety update, Lundbeck identified 11/30/10 as the cutoff date for the majority of safety data and used the cutoff date of 3/11/11 for deaths in trial OV-1004.

7.1.2 Categorization of Adverse Events

Lundbeck explained that they used the Medical Dictionary for Regulatory Activities (MedDRA) version 12.0 to code investigator verbatim terms to preferred terms for use in AE analyses (ISS, p.41). In their AE data sets, Lundbeck provided the investigator verbatim terms and the preferred terms for all AEs. I reviewed the AE data set to assess the AE term coding process. In general, the coding process seemed appropriate and allowed for reliable estimates of AE risks.

There were few instances where the coding process appeared to result in splitting of likely related events into separate preferred terms but Lundbeck adequately addressed these in subsequent analyses. MedDRA 12.0 allowed for verbatim terms describing sedation or sleepiness, commonly observed AEs, to be coded to a number of different preferred terms including somnolence, hypersomnia, sedation, lethargy and depressed level of consciousness. To address this finding, the Division required Lundbeck to submit additional analyses that grouped the preferred terms listed above as sedation-related events. Lundbeck also provided analyses that estimated the frequency of these events and described the onset, duration, and predictive factors. Similarly, pneumonia verbatim terms could be coded to a number of different preferred terms. When Lundbeck conducted additional analyses for these events, they included all AEs of pneumonia.

In a 6/30/11 submission, Lundbeck notified the Division of errors in their AE presentations in the ISS and 120 day Safety Update. Lundbeck included 30 AEs that occurred in the RCTs OV-1002 and OV-1012 with AEs from the open label extension trial OV-1004. Lundbeck corrected and resubmitted the AE tables and the AE datasets. Lundbeck also provided a listing of the 30 AEs that they mistakenly identified as from OV-1004. I reviewed the listing and found that 21 events were from OV-1002 and 9 from OV-1012. There did not appear to be a cluster of similar AEs and therefore this mistake would not have altered the conclusions based on AE risk comparisons included with the ISS and 120 day Safety Update. I checked the AE presentations for the controlled trials from the previous submissions, and updated any tables that changed based on the 6/30/11 submission.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In their analyses, Lundbeck pooled the Phase I trials safety data. This approach is reasonable because of the generally short duration of exposures in these trials and similar characteristics of the exposed population (generally health adults). Given that there were only 2 phase II/III controlled trials, and that only 1 trial had a placebo control, Lundbeck presented separately the safety data from Trial OV-1002 and OV1012. Lundbeck also provided analyses of safety data for all clobazam exposed LGS subjects (pooled from the 2 controlled trials and the open label extension). These analyses provide overall summaries of the experience over time but are limited in that they do not allow for comparative risk analyses and include the experience in the relatively short term controlled trials and the long term open label experience.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Considering only the trials that were conducted by Lundbeck, the exposure in the clobazam NDA does not meet the ICH guideline recommendations. Lundbeck reported that in their development program trials, 633 subjects were exposed to clobazam. Of this group, 253 subjects were exposed to clobazam for at least 6 months, and 197 for at least 12 months (Safety Update, p.17). Inclusion of legacy trials in exposure estimates increases the total number of unique patients exposed to clobazam but since many of these trials lack "...dose, start date, and stop date" (Summary of Clinical Safety, p.17) they cannot provide complete information about exposure by duration or by dose and duration. In addition, as noted above, these trials did not prospectively define or capture SAEs.

Number of Unique Subjects Exposed

Lundbeck stated that their NDA included safety data for 2236 unique clobazam exposed study subjects. In Lundbeck-conducted Phase I-III trials, 633 subjects were exposed to clobazam (Phase I n=333, Phase II/III n=300). Lundbeck noted that the remaining study subjects were exposed to clobazam in the legacy trial 301 (n=119) and in the legacy psychiatry trials (n=1484).

Exposure by Duration

In their Table 3, Lundbeck summarized the exposure by duration for clobazam clinical trials through the 120 day safety update cutoff. I include that table below.

Table 3. Estimated Clobazam Exposures in Unique Subjects (30 November 2010)

Duration of clobazam exposure	Total	Phase 1 Trials	Phase 2/3 LGS Trials	Legacy Epilepsy Trial 301	Legacy Psychiatry Trial ¹
At least 1 dose	1847	333	300	119	1095*
6 months	357	N/A	253	80	24
12 months	243	N/A	197	45 ²	1
24 months	100	N/A	100	N/A	N/A

120 day Safety Update, p.17, NA = not applicable

*Total includes only those subjects with exposure data

¹ Due to the lack of available study drug start and stop dates, the Legacy Psychiatry Trials were not summarized according to exposure, but rather according to length of observation.

² The discrepancy between 12-month clobazam exposure (N=45) and subjects who completed the trial (N=65) is likely due to the fact that exposure is a calculated value from dosing records, while disposition of subjects was determined by the Investigator, recorded separately, and may have been impacted by shortened visit windows.

Lundbeck noted that exposure data for legacy Psychiatry trials is incomplete. The percentage of subjects lacking exposure data ranged from 1.5% in US and Canadian controlled trials to 86% in a subset of uncontrolled trials (ISS, p.76). The table below summarizes the availability of exposure data, using Lundbeck's groupings of legacy Psychiatry trials.

Summary of exposure data availability for clobazam legacy Psychiatry Trials

Trial grouping	Assigned to clobazam (n)	With start/stop dates (n/%)	With some exposure data [*] (n/%)	With no exposure data (n/%)
US/Canadian Controlled trials	203	142 (70%)	58 (29%)	3 (1%)
Rest of World Controlled trials	395	10 (3%)	221 (56%)	164 (41%)
Controlled non CRF trials	615	516 (84%)	19 (3%)	80 (13%)
Uncontrolled CRF trials	200	0	119 (60%)	81 (40%)

Uncontrolled non CRF trials	71	0	10 (14%)	61 (86%)
Total	1484	668 (45%)	427 (29%)	389 (26%)

*Includes patients with start date but no stop date and patients with no start or end date but some reference date

From ISS tables 2.4.1.1, 2.4.2.1, 2.4.3.1, 2.4.4.1, 2.4.5.1

For the 1095 subjects in legacy Psychiatry trials with complete or some exposure data, 24 were exposed to clobazam for at least 180 days and 1 was exposed for at least 360 days. For these same subjects, 44 were exposed to a clobazam dose <20mg/day, 368 were exposed to a dose between 20mg and 40mg/day, and 683 were exposed to a dose between 40 and 60mg/day (from ISS tables 2.4.1.2, 2.4.2.2, 2.4.3.2, 2.4.4.2, and 2.4.5.2).

Demographics

In Phase I trials conducted by Lundbeck, no pediatric patients (<=16 years of age) were enrolled. The mean age of participants in these trials was 36 years (median 35.7 years, range 18-74 years). Lundbeck reported that 60% (210/349) of participants were male and that 78% (272/349) were white (ISS table 3.1.1).

Lundbeck presented the demographic data for their Phase II/III trials OV-1002 and OV-1012 separately (OV-1004, the third trial conducted by Lundbeck was the open label extension trial that included patients from OV-1002 and OV-1012). In both trials, the patients were predominately males, in the pediatric age group, and white. The following table summarizes demographic data from the two trials.

Baseline Demographic Characteristics of Subjects in Trials OV-1002 and OV-1012

Parameter	Statistic	Trial OV-1002		Trial OV-1012			
		Clobazam 0.25mg/kg (n=32)	Clobazam 1mg/kg (n=36)	Placebo (n=59)	Clobazam 0.25mg/kg (n=58)	Clobazam 0.5mg/kg (n=62)	Clobazam 1mg/kg (n=59)
Age (years)	N	32	36	59	58	62	59
	Mean	9.2	8.5	13.0	10.9	14.1	11.7
	Median	8.3	7.2	10.4	9.0	11.4	9.1
	Min	1.8	2.1	2.6	2.3	2.5	2.2
	Max	25.7	22.6	54	33.7	49.2	38.6
Sex (male)	% (n)	59% (19)	64% (23)	64% (38)	62% (36)	58% (36)	58% (34)
Race							
White	% (n)	78% (25)	94% (34)	71% (42)	57% (33)	57% (35)	63% (37)
Asian	% (n)	3% (1)	0	22% (13)	28% (16)	26% (16)	27% (16)
Other	% (n)	19% (6)	6% (2)	7% (4)	15% (9)	18% (11)	10% (6)

From ISS Table 3.1.2

In the legacy epilepsy trial 301, the average age of subjects in the clobazam group (7.6 years) was similar to the average age of subjects in the active comparator group (8.1

years). The percentage of males in the clobazam group (59%) was slightly higher than the percentage of males in the active comparator group (52%). Race data was not recorded for subjects in this trial (ISS table 3.1.2). The legacy Psychiatry studies enrolled primarily adult subjects (mean age range from 29.19-42.33 years) and in the studies that recorded sex, a majority of subjects were females (ISS, p.81).

7.2.2 Explorations for Dose Response

Exposure by Dose and Duration

In their proposed labeling, Lundbeck recommends consideration of body weight when dosing clobazam. For patients ≤ 30 kg, Lundbeck recommends a starting dose of clobazam of 5mg/day with a target total daily dose of 10-20mg (administered in divided doses, twice daily). For patients >30 kg, Lundbeck recommends a starting dose of clobazam of 10mg/day with a target total daily dose of 20-40mg (administered in divided doses, twice daily). Lundbeck does not identify a maximum clobazam dose, but does propose stating in labeling that doses up to 80mg/day have been administered in uncontrolled trials in patients with LGS.

In their 120 day Safety Update, Lundbeck provided Table 4 summarizing exposure by dose and duration for their Phase II/III trials. This table summarized dose as mg/kg/day. In practice, clobazam will be dosed in mg/day. To translate dose in mg/kg/day to daily dose in mg, Lundbeck considered low dose as .25mg/kg (up to 10mg/day), medium dose as 0.5mg/kg (up to 20mg/day), high dose as 1mg/kg (up to 40mg/day) and maximum dose as >1 mg/kg (80mg/day). I provide Table 4 below.

Table 4. Clobazam Modal and Maximum Daily Dose for Phase 2/3 LGS Studies

Daily Dose (mg/kg)/ Subject	Days of Exposure									
	≥ 1		≥ 30		≥ 90		≥ 180		≥ 360	
	ISS (N = 300)	SU (N = 300)	ISS (N = 285)	SU (N = 285)	ISS (N = 264)	SU (N = 264)	ISS (N = 253)	SU (N = 253)	ISS (N = 193)	SU (N = 197)
Modal										
Mean (SD)	0.859 (0.500)	0.869 (0.510)	0.872 (0.503)	0.882 (0.513)	0.892 (0.510)	0.903 (0.520)	0.907 (0.512)	0.919 (0.522)	0.958 (0.512)	0.959 (0.518)
Min, Max	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72	0.06, 2.72
Maximum										
Mean (SD)	1.073 (0.569)	1.108 (0.578)	1.097 (0.568)	1.134 (0.576)	1.134 (0.569)	1.173 (0.575)	1.155 (0.568)	1.195 (0.574)	1.218 (0.578)	1.245 (0.578)
Min, Max	0.17, 4.81	0.17, 4.81	0.19, 4.81	0.19, 4.81	0.25, 4.81	0.25, 4.81	0.25, 4.81	0.25, 4.81	0.25, 4.81	0.25, 4.81
Daily Dose (mg/kg)/ Subject	Days of Exposure									
	≥ 540		≥ 720		≥ 900		≥ 1080		≥ 1440	
	ISS (N = 130)	SU (N = 137)	ISS (N = 95)	SU (N = 100)	ISS (N = 57)	SU (N = 59)	ISS (N = 49)	SU (N = 49)	ISS (N = 45)	SU (N = 45)
Modal										
Mean (SD)	0.983 (0.522)	0.978 (0.525)	0.989 (0.536)	0.977 (0.529)	0.985 (0.529)	0.980 (0.516)	0.947 (0.494)	0.947 (0.495)	0.969 (0.503)	0.970 (0.503)
Min, Max	0.18, 2.72	0.18, 2.72	0.18, 2.72	0.18, 2.72	0.22, 2.72	0.22, 2.72	0.22, 2.72	0.22, 2.72	0.22, 2.72	0.22, 2.72
Maximum										
Mean (SD)	1.250 (0.533)	1.271 (0.540)	1.280 (0.562)	1.297 (0.550)	1.274 (0.573)	1.293 (0.559)	1.196 (0.476)	1.201 (0.462)	1.210 (0.495)	1.215 (0.479)
Min, Max	0.25, 3.33	0.25, 3.33	0.25, 3.33	0.25, 3.33	0.25, 3.33	0.25, 3.33	0.25, 2.72	0.25, 2.72	0.25, 2.72	0.25, 2.72

ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; SD = standard deviation; SU = Safety Update

Note: A subject's modal dose was the TDD that was received on the largest number of days. If 2 or more TDDs were received the same number of days for a subject, the highest dose was assigned.

Source: ISS Tables 2.2.2 and Safety Update Table 2.2.2

Table 4 demonstrates that when considering either the modal or maximum dose, these 300 subjects were exposed to clobazam doses in the sponsor's proposed recommended range.

In legacy epilepsy trial 301, the mean modal dose for the 80 subjects exposed for at least 180 days was 0.673mg/kg (ISS table 22). For the 80 subjects exposed at least 180 days, 3 subjects were in the low dose group (.25mg/kg, up to 10mg/day), 57 in the medium dose group (0.5mg/kg, up to 20mg/day), 16 in the high dose group (1mg/kg, up to 40mg/day) and 4 in the maximum dose group (>1mg/kg, 80mg/day) (ISS table 23).

7.2.3 Special Animal and/or In Vitro Testing

As part of their cardiovascular safety pharmacology evaluation for clobazam, Lundbeck conducted in vitro and animal studies. Lundbeck examined the effects of clobazam and its major metabolite N-CLB on I_{Kr} in HEK293 cells. Lundbeck also studied the effect of clobazam and N-CLB on modulation of electrophysiologic properties of isolated rabbit Purkinje fibers. In addition, Lundbeck evaluated the effect of clobazam, administered as single doses, on blood pressure, heart rate, and cardiac electrophysiology in conscious dogs.

Lundbeck found that Clobazam displayed a concentration dependent inhibition of I_{Kr} ranging from 18% to 52% from 2.5 μ M to 250 μ M. While N-CLB inhibited hERG currents by up to 48% when tested at concentrations ranging from 1 to 125 μ M. These results suggested that if either compound alone or the two compounds in combination achieve free plasma concentrations in the range of 1 to 2.5 μ M (\geq 300 ng/mL), prolongation of the QT interval might be evident. However, both clobazam and N-CLB caused a concentration dependent decrease in the action potential duration in isolated rabbit Purkinje fibers. Lundbeck felt that the finding of APD shortening is most consistent with inhibition of other, non I_{Kr} cardiac ion channels leading to a likely overall lack of significant effect on QT prolongation (Non-clinical overview, p.11).

In the dog study, Lundbeck reported a decrease in blood pressure at the highest dose tested (50 mg/kg) but no effects at 1 or 10 mg/kg. Lundbeck also noted a reflex increase in heart rate, presumably in response to mild decreases in blood pressure. Lundbeck did not consider the changes in blood pressure and heart rate adverse as they remained within or near historical control ranges. Lundbeck found that Clobazam was not associated with changes in the QT and QTc intervals. Based on extrapolation of toxicokinetic information from the 28-day toxicity evaluation in dogs, a dose of 50 mg/kg clobazam is unlikely to exceed total C_{max} values of 560 ng/mL (1.86 μ M). In contrast to the parent, N-CLB free plasma C_{max} in the conscious dog cardiovascular study was estimated to be 23 μ M (6900 ng/mL) and is probably at concentrations where alterations of cardiac ion channels may be observed (Non-clinical overview, p.11).

Based on the results of the rabbit Purkinje fiber study, both clobazam and N-CLB were associated with minor shortening of the APD₆₀ and APD₉₀, consistent with activity at cardiac ion channels other than hERG. Lundbeck felt that these results may explain why changes in QT and QTc were not evident in the telemetered dog study as the activity of these compounds at other ion channels may have mitigated their activity on I_{Kr}, with no observable effect on cardiac conduction (Non-clinical overview, p.12).

7.2.4 Routine Clinical Testing

Phase I trials

The clinical testing included in the Phase I trial protocols appeared adequate to allow assessment of the safety of clobazam. During Phase I trials, Lundbeck captured AEs from the first dose of study drug through 30 days after the last dose. In addition, Lundbeck collected hematology, chemistry and urinalysis samples. The number of laboratory and vital sign data measurements was dependent on trial design and duration, with shorter trials having fewer data measurements for a given subject. All Phase I trials included at least one pretreatment (screening or baseline) and one on treatment ECG (ISS, pp.31-31).

Phase II/III

The clinical testing in the Phase II/III trial protocols appeared adequate to allow assessment of the safety of clobazam. During Phase II/III trials, Lundbeck captured AEs from the first dose of study drug through 30 days after the last dose. During trial OV-1002, investigators collected hematology, chemistry, and urine samples at baseline, week 3 (end of titration), week 7, and week 11 (end of taper). In trial OV-1012, investigators collected hematology, chemistry, and urine samples at baseline, week 3 (end of titration), week 7, week 11, and week 15 (end of taper). During trial OV-1004 (open label extension) Lundbeck collected hematology, chemistry, and urine samples on day 1, month 6, and then every 6 months thereafter. Lundbeck also collected samples at final visits (1 week after last dose). Lundbeck collected vital sign data at each trial visit. In trial OV-1002, Lundbeck collected ECGs at screening and week 7. In trial OV-1012, Lundbeck collected ECGs at screening, day -1, and week 5 (1-2 hours predose, 2-4 hours post dose), week 7, and week 15. In OV-1004, Lundbeck collected ECGs on day 1 and then yearly thereafter (ISS, p.32).

I summarize the lab and vital sign data captured during the Phase II/III trials in the following table.

Laboratory and Vital Sign Data Captured During Phase II/III Clobazam Trials

Hematology	hematocrit, hemoglobin, MCHC, MCV, RBCs, WBCs/differential, platelets,
Chemistry	albumin, ALP, ALT, AST, BUN, calcium, bicarbonate, chloride, creatinine, direct bilirubin, glucose, magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid

Urinalysis	pH, ketones, leukocytes, protein, urine glucose, urine microscopy
Vital signs	Systolic blood pressure, diastolic blood pressure, pulse

7.2.5 Metabolic, Clearance, and Interaction Workup

Lundbeck reported that following oral administration, clobazam is rapidly and completely absorbed and extensively metabolized. The time to peak concentrations (T_{max}) ranged from 0.5 to 4 hours.

Lundbeck explained that clobazam undergoes dealkylation to the active metabolite N-CLB. CYP3A4/5 is primarily responsible for this biotransformation but CYP2C19 and CYP2B6 have the potential to metabolize clobazam as well. Biotransformation of N-CLB is mediated by CYP2C19 (Non-Clinical Overview, p.16). Less than 1% of a clobazam dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine. Lundbeck noted that based on population pharmacokinetic analyses, the median half-lives of clobazam and N-desmethylclobazam were estimated to be 36 and 79hr, respectively.

In proposed labeling, Lundbeck would state that the systemic exposure (AUC) of clobazam is comparable between CYP2C19 poor and extensive metabolizers. In extensive metabolizers, steady state plasma exposure of N-desmethylclobazam is approximately 3 fold higher than that of clobazam. CYP2C19 poor metabolizers have approximately 5 fold higher plasma exposure of N-desmethylclobazam as compared to that of extensive metabolizers. Lundbeck would not recommend genotyping patients for CYP2C19 polymorphisms prior to clobazam treatment. Lundbeck feels that “recommended dose titration to achieve a clinically meaningful effect obviates the need to genotype patients for CYP2C19 polymorphism prior to initiating clobazam therapy.” (Summary of Clinical Safety, p.63).

Lundbeck’s exploration for drug-drug interactions for clobazam included analyses of select Phase I trials, and review of population PK modeling data. Lundbeck reported their findings by summarizing data pertinent to specific cytochrome P450 isoform and the effect of the coadministered drug(s) (induction vs. inhibition). Lundbeck first looked at the effect of other drugs on clobazam and N-CLB, and then looked at the effect of clobazam on other drugs. Lundbeck also reviewed interaction data for valproic acid and lamotrigine (see section 7.5.5).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Below I summarize side effects of the benzodiazepines as identified from The Pharmacologic Basis of Therapeutics.

- Effects of benzodiazepines that are the basis for clinical use include sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity.
- Benzodiazepines can have non CNS effects such as coronary vasodilation, with intravenous administration of therapeutic doses of certain benzodiazepines, and neuromuscular blockade, with very high doses.
- Hypnotic doses of benzodiazepines in normal subjects generally do not affect respiration, but benzodiazepines can depress alveolar ventilation, as the result of a decrease in hypoxic drive, in patients with COPD.
- Benzodiazepines can cause apnea during anesthesia or when given with opioids. Patients severely intoxicated with benzodiazepines and other CNS-depressant drugs (ex, ethanol) may require respiratory assistance.
- Hypnotic doses of benzodiazepines may worsen sleep-related breathing disorders by adversely affecting control of the upper airway muscles or by decreasing the ventilatory response to CO₂. In patients with obstructive sleep apnea (OSA), hypnotic doses of benzodiazepines may decrease muscle tone in the upper airway and exaggerate the impact of apneic episodes on alveolar hypoxia, pulmonary hypertension, and cardiac ventricular load.
- Hypnotic doses of benzodiazepines can cause light-headedness, lassitude, increased reaction time, motor incoordination, impairment of mental and motor functions, confusion, anterograde amnesia, weakness, headache, blurred vision, vertigo, nausea and vomiting, epigastric distress, and diarrhea.
- Benzodiazepines may cause paradoxical effects including increases the incidence of nightmares, garrulousness, anxiety, irritability, tachycardia, sweating, amnesia, euphoria, restlessness, hallucinations, sleep-walking, sleep-talking, hypomanic behavior, bizarre uninhibited behavior, hostility and rage.
- Chronic benzodiazepine use poses a risk for development of dependence and abuse. Withdrawal symptoms may include temporary intensification of the problems that originally prompted their use (e.g., insomnia or anxiety), dysphoria, irritability, sweating, unpleasant dreams, tremors, anorexia, and faintness or dizziness.
- When taken alone, even high doses of benzodiazepines are rarely fatal. Concomitant ethanol is a common contributor to deaths involving benzodiazepines, and true coma is uncommon in the absence of another CNS

depressant. Overdosage with a benzodiazepine rarely causes severe cardiovascular or respiratory depression.

- Large doses of benzodiazepines taken just before or during labor may cause hypothermia, hypotonia, and mild respiratory depression in the neonate. Abuse by the pregnant mother can result in a withdrawal syndrome in the newborn.
- Reports of clinically important pharmacodynamic interactions between benzodiazepines and other drugs have been infrequent. Ethanol increases both the rate of absorption of benzodiazepines and the associated CNS depression.

Aside from withdrawal, Lundbeck did not specifically evaluate study subjects for many of the known benzodiazepine associated AEs listed above. Lundbeck did require for their clinical trials that narratives be written for all AEs suggestive of withdrawal that were observed after stopping clobazam. In addition, in Phase I trials OV-1022, OV-1023, and OV-1038, investigators administered the Clinical Institute Withdrawal Assessment for Benzodiazepine (CIWA-B) questionnaire to study subjects.

Mihic S. John, Harris R. Adron, "Chapter 17. Hypnotics and Sedatives" (Chapter). Brunton LL, Chabner BA, Knollmann BC: Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e: <http://www.accessmedicine.com/content.aspx?aID=16663643>.

7.3 Major Safety Results

7.3.1 Deaths

Mortality Risks

Through the 120 day Safety Update, across Lundbeck's development program and the legacy trials, investigators reported 9 deaths in clobazam exposed subjects (0.4%, 9/2236). Seven deaths were reported in the ISS and two additional deaths were reported in the 120 day Safety Update.

No deaths occurred during Lundbeck's Phase I trials, or randomized controlled LGS trials OV-1002 or OV-1012. All 9 deaths in clobazam subjects (3%, 9/300) occurred during Lundbeck's open label extension trial OV-1004.

The only death reported from the legacy epilepsy trial 301 occurred in a comparator group subject (carbamazepine). The only death reported from the legacy Psychiatry

trials occurred during trial 410, in a subject taking placebo (Summary of Clinical Safety, p.35).

Deaths in Trial OV-1004

As noted above, investigators reported 9 deaths in clobazam treated patients enrolled in the open label extension trial OV-1004. Five of these patients were male and four were female. The ages of those who died were 4 (n=2), 5, 7, 8, 12, 19, 22, and 36 years. The total daily clobazam doses taken at the time of the event for the patients who died were 10mg, 20mg, 30mg (n=2), 35mg (n=2), 40mg, and 50mg (n=2).

The most commonly reported cause of death was pneumonia (n=3). One additional patient died while receiving hospice care following a hospitalization for pneumonia and dehydration. Three patients died at home and did not have a clearly identified cause of death (death n=2, epilepsy). One patient died during hospitalization for seizures and the reported cause of death was respiratory failure. One patient died during a hospitalization for a hematoma and urosepsis. All 9 subjects who died had severe neurological disabilities. In the following paragraphs, I summarize available clinical details for the 9 deaths in patients treated with clobazam.

Subject 0017-0107, a 5 year old male treated with clobazam for 1021 days, died at home and no details about his death were available. The subject received clobazam in preceding RCT OV-1002 and total daily clobazam dose at the time of death was 30mg. The subject was treated for LGS and his medical history prior to entering the trial was significant for microcephaly, plagiocephaly, severe developmental disability, obstructive sleep apnea, GERD, inability to verbalize with minimal response to social stimuli, increased muscular tone in extremities, inability to ambulate, inability to sit or stand, ankle clonus, infantile spasms, and failure to thrive. Concomitant medications/treatments during the trial were BIPAP, pseudophedrine, panadeine co, amoxicillin, lidocaine, morphine, ringers lactate, heparin, dexamethasone, vecuronium, sevoflurane, azithromycin, paracetamol, trimethoprim, varicella vaccine, MMR vaccine, Hep A vaccine, fluconazole, glucose, nystatin, budesonide, levosalbutamol, ciprofloxacin, macrogol, lansoprazole, epinephrine, midazolam, cefazolin, ceftriaxone, cefotaxime, enemas, laxatives, lamotrigine, levetiracetam, lorazepam, and phenobarbital. AEs reported during the trial included hospitalization for sleep apnea, drug interaction (the investigator felt fluconazole and either clobazam or lamotrigine resulted in stupor), aspiration, dehydration, oral candidiasis, pneumonia, ear infection, nasal congestion, upper respiratory tract infection, sinusitis, otitis media, swallowing dysfunction and G-tube placement, and dental carries.

Subject 0018-0607, a 22 year old female treated with clobazam for 1318 days, died unexpectedly during her sleep and the reported cause of death was epilepsy. This subject received clobazam in preceding RCT OV-1002 and total daily clobazam dose at the time of death was 50mg. This subject was treated for LGS and her medical history prior to entry in the trial was significant for mental retardation, inability to verbalize, obstructive sleep apnea, neonatal apnea, tonsillectomy, adenoidectomy, uvulectomy, right foot aversion, bruised right leg, and burn injuries. Concomitant medications/treatments included lamotrigine and VNS.

Subject 0008-7059, a 4 year old female treated with clobazam for 305 days, was found at home in cardiopulmonary arrest and did not respond to resuscitation efforts. The investigator was told that the autopsy determined that the cause of death was "natural causes" with underlying seizure disorder related to perinatal asphyxia. This subject received clobazam in preceding RCT OV-1012 and total daily clobazam dose at the time of death was 35mg. This subject was treated for LGS and her medical history prior to entry in the trial was significant for severe mental retardation, severe spastic cerebral palsy,

infantile spasms, encephalopathy, generalized brain edema, cephalhematoma, right sided vessel hematoma, microcephaly, hypsarrhythmia, severe developmental delay, failure to thrive, perinatal asphyxia, diminished coordination, no normal reflexes, decreased alertness, cortical blindness, dry eyes and lips, swallowing dysfunction, bilateral serous otitis, pharyngitis, trouble clearing secretions, aspiration pneumonia, G-tube placement, chronic constipation, GERD, Nissan fundoplication, hypotonia, non-ambulatory, wheelchair bound, hyperreflexia, generalized spasticity, spastic quadraparesis, bilateral hip clicking, diaper rash, reaction to levetiracetam and felbamate (nausea and vomiting), left arm and left shoulder click, hypoxic ischemic injury, and Sandifer syndrome. Concomitant medications included metoclopramide, simethicone, budesonide, magnesium hydroxide, glycopyrronium, bisacodyl, ranitidine, ipratropium salbutamol, amoxicillin, bacitracin, valproic acid, topiramate, and zonisamide.

Subject 0812-7071, a 7 year old female treated with clobazam for 191 days, died and the reported cause of death was pneumonia. This subject received clobazam in preceding RCT OV-1012 and total daily clobazam dose at the time of death was 10mg. The patient was hospitalized for pneumonia and the only clinical detail reported was that she required a blood transfusion. This subject was treated for LGS and her medical history prior to entry in the trial was significant for hypotonia, infantile spasms, severe malnutrition, and lamotrigine allergy. The only identified concomitant medication was valproic acid. This patient had an AE of somnolence that was noted approximately 1 month prior to, and was continuing at the time she developed pneumonia.

Subject 0032-8051, a 19 year old male treated with clobazam for 497 days, died and the cause of death was pneumonia, sepsis, and acute respiratory distress syndrome. The subject experienced an extended seizure with aspiration and developed a fever and was subsequently hospitalized for pneumonia. He developed acute respiratory distress syndrome. His course was notable for worsening acidemia, hypotension requiring vasopressors and, bradycardia and absent pulse requiring CPR. The family decided to stop heroic measures and the subject died. The subject received clobazam in the preceding RCT OV-1012 and the total daily dose at the time of death was 35mg. He was treated for LGS and medical history prior to entering the trial included focal status epilepticus, cognitive impairment, developmental delay, drooling, tachypnea, cough, rales, obesity, dry skin, seasonal allergies, and constipation. Concomitant medications were glycopyrronium, loratidine, mometasone, macrogol, topiramate, felbamate, diazepam, and lorazepam. This patient did not have recorded AEs of somnolence or sedation during his treatment with clobazam.

Subject 0700-8060, an 8 year old male treated with clobazam for 183 days, died and the cause of death was respiratory insufficiency due to bilateral pneumonia that resulted from aspiration. The subject was admitted to an ICU for bilateral pneumonia and was treated with antibiotics. He required mechanical ventilation for 18 days. He was extubated but had weak cough and continuing signs of respiratory insufficiency. The patient experienced “decompensation of vital functions” and subsequently died. The subject received clobazam in the preceding RCT OV-1012 and he was receiving a total daily dose of 40mg at the time of death. He was being treated for LGS and medical history prior to entering the trial included aspiration, tachypnea, rales, cough, severe mental retardation, poor coordination, dysmorphic face, conjunctivitis, obesity, repeated bronchitis, autism, hydrocephalus, hypothyreosis, right adrenal gland abnormality, and generalized tonic clonic status epilepticus. He was diagnosed with hypopituitarism during the trial. Concomitant medications were levothyroxine, benzylpenicilin, salbutamol, paracetamol, cefuroxime, cefazolin, omeprazole, furosemide, prednisolone, ipratropium, pipecuronium, valproic acid, topiramate, and diazepam. This patient had an AE of somnolence that began more than 4 months prior to and resolved 3 months prior to developing pneumonia.

Subject 0038-7002, a 12-year-old male with LGS, treated with clobazam for 1111 days, died in hospice care following a hospital admission for pneumonia and dehydration. He was receiving a total clobazam daily dose of 20mg at the time of the pneumonia and dehydration AEs. Relevant medical history included mental retardation, status epilepticus, cerebral palsy, microcephalic, cortical blindness, drooling, pneumonia, asthma, constipation, G-tube placement, vagal nerve stimulator placement, incontinence,

spastic quadriparesis with contractures in upper and lower extremities, scoliosis, lordosis, kyphosis, and CVA. Concomitant medications recorded during the time of the event included lactulose, bisacodyl, ciprodex, botulinum toxin type A, nystatin, acetylcysteine, azithromycin, salbutamol, mupirocin, duoderm, paracetamol, and magnesium. AEDs administered during the trial included lamotrigine, phenytoin, topiramate, and lorazepam. On Day 1108, the subject was hospitalized with pneumonia/dehydration. The subject was put on do not resuscitate status on Day 1109 and returned home under hospice care on Day 1111. All oral tablet medications including clobazam were discontinued. The subject died on Day 1117.

Subject 0046-7062, a 4 year old male treated with clobazam for 514 days, died and the cause of death was respiratory failure. He was receiving a total daily clobazam dose of 50mg at the time of death. The subject was hospitalized for convulsions and after clinical seizures ceased, EEG found ongoing subclinical seizures. The subject's hospital course was also notable for UTI and desaturation episodes. The subject had a salvagram that demonstrated aspiration. His G tube was converted to a GJ tube. He subsequently experienced respiratory failure and died. He was treated for LGS and medical history prior to entering the trial included mental retardation, bradycardia, cortical blindness, hypotonia, infantile spasms, progressive myoclonic epilepsy, GERD, generalized weakness, weight loss, somnolence, and periods of insomnia. Concomitant medications were lansoprazole, ranitidine, montelukast, vitamin D, macrogol, citric acid, melatonin, glycopurronium, levetiracetam, topiramate, and rufinamide.

Subject 0504-8030, a 36-year-old female with LGS, treated with clobazam for 948 days, died during a hospitalization for urosepsis and right leg hematoma. She was receiving a total daily clobazam dose of 30mg at the time of death. Relevant medical history included cerebral palsy, left hemiparesis, bilateral spastic quadriparesis, severe intellectual impairment, corpus callosotomy, recurrent urinary tract infections, osteoarthritis, and chronic constipation. Concomitant medications recorded during the time of the event included lactulose, metamucil, and chondrosamine with MSN. AEDs administered during the trial included carbamazepine, valproic acid, levetiracetam, clonazepam, and phenytoin. She was admitted to the hospital via the emergency department on Day 944 following increased lethargy, poor oral intake, large hematoma on right leg, sepsis from suspected urinary tract infection, hypotension, anemia, and valproate toxicity. Laboratory results on Day 944 included a hemoglobin of 90 g/L (normal range: 115-150), WBC count of 14.6 x 10⁹/L (normal range: 4.0-11.0), platelet count of 127 x 10⁹/L (normal range not provided), and red blood cell count of 2.92 x 10¹²/L (normal range: 3.80-5.10). A CT image showed a large collection of blood in right leg on Day 945. The subject received blood transfusion on Day 945 and was transferred to the intensive care unit. The subject died on Day 948. The cause of death was unknown at the time of reporting. The investigator considered the events not related to clobazam and alternative etiology was unknown, questionable thrombocytopenia and poor mobility.

She experienced a non-serious AE of thrombocytopenia on Day 647. The subject had normal screening (201 Gi/L) and baseline (163 Gi/L) platelet counts in the preceding RCT OV-1012. Platelet counts fluctuated on treatment during OV-1012 (day 21 160 Gi/L, day 49 98 Gi/L, and day 77 129 Gi/L). In trial OV-1004, she had low platelet counts on Day 105 (121 Gi/L), Day 282 (106 Gi/L), Day 477 (104 Gi/L), and Day 644 (86 Gi/L) (normal range: 140-400 Gi/L). No additional platelet counts were available for the trial.

Although there were 5 deaths with respiratory etiologies (respiratory failure, pneumonia), these patients had underlying medical conditions (neurological disabilities, documented aspiration, gastroesophageal reflux, feeding tubes, etc.) that put them at high risk of respiratory disorders and infections. Three of the pneumonia death narratives mentioned aspiration (2 following seizures). These underlying risk factors complicate the assessment of the role of clobazam in these events.

7.3.2 Serious Adverse Events

Phase I Trials

Lundbeck stated that there were no SAEs reported in their Phase I trials (Summary of Clinical Safety, p.36).

Phase II/III Trials

In their Phase II/III Trials (RCTs OV-1002, OV-1012, and open label extension trial OV-1004) through the Safety Update cutoff, Lundbeck reported that 34% (103/300) of clobazam exposed subjects experienced one or more treatment emergent SAEs (Safety Update, p.28). The System Organ Class for which most subjects had an SAE was Infections and Infestations (17.3%, n=52) and the most common SAE was Pneumonia (8.7%, n=26). In the following table I identify those SAEs that occurred in 2 or more clobazam exposed subjects.

Treatment Emergent SAEs Reported by at least 2 subjects in the Phase II/III Clobazam Trials

Treatment Emergent SAE	Clobazam N=300
Any	34% (103)
Pneumonia	8.7% (26)
Convulsion	7.0% (21)
Pneumonia aspiration	3.3% (10)
Lobar pneumonia	2.3% (7)
Status epilepticus	2.0% (6)
Urinary tract infection	2.0% (6)
Grand mal convulsion	1.7% (5)
Lennox-Gastaut syndrome	1.7% (5)
Pyrexia	1.7% (5)
Sleep apnea syndrome	1.7% (5)
Constipation	1.3% (4)
Dehydration	1.3% (4)
Gastroenteritis	1.3% (4)
Therapeutic agent toxicity	1.3% (4)
Vomiting	1.3% (4)
Cellulitis	1.0% (3)
Decubitus ulcer	1.0% (3)
Influenza	1.0% (3)
Petit mal epilepsy	1.0% (3)
Respiratory distress	1.0% (3)
Sepsis	1.0% (3)
Thrombocytopenia	1.0% (3)
Vagal nerve stimulator implant	1.0% (3)
Aspiration	0.7% (2)

Bronchopneumonia	0.7% (2)
Death	0.7% (2)
Epilepsy	0.7% (2)
Otitis media	0.7% (2)
Femur fracture	0.7% (2)
Gastroenteritis viral	0.7% (2)
Hypoxia	0.7% (2)
Implant site infection	0.7% (2)
Muscle contracture	0.7% (2)
Myoclonic epilepsy	0.7% (2)
Oral candidiasis	0.7% (2)
Pancreatitis	0.7% (2)
Pneumonia viral	0.7% (2)
Respiratory failure	0.7% (2)
Scoliosis	0.7% (2)
Septic shock	0.7% (2)
Talipes	0.7% (2)
Tooth abscess	0.7% (2)
Tracheitis	0.7% (2)
Tonsillar hypertrophy	0.7% (2)
Viral infection	0.7% (2)
Viral tracheitis	0.7% (2)

From 120 day Safety Update Table 9, pp.28-29.

There was one SAE of hepatic enzyme increased. There were no SAEs coded to the following preferred terms: aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, acute renal failure, acute liver failure, rhabdomyolysis, angioedema, or anaphylaxis.

In Lundbeck's RCT OV-1002, 6.3% (2/32) of the clobazam low dose patients experienced an SAE compared to 8.3% (3/36) of the high dose patients.

In RCT OV-1012, 3.4%, (2/59) of subjects in the placebo group experienced an SAE compared to 5.2% (3/58) in the low dose clobazam group, 9.7% (6/62) in the medium dose clobazam group, and 8.5% (5/59) in the high dose clobazam group.

In the following table, I summarize the SAEs from Lundbeck's Phase II/III RCTs.

Treatment Emergent SAEs from Double Blind Phase II/III Trials OV-1002, OV-1012

SAE	Trial OV-1002		Trial OV-1012			
	Clobazam 0.25mg/kg N=32	Clobazam 1.0 mg/kg N=36	Placebo N=59	Clobazam 0.25mg/kg N=58	Clobazam 0.50mg/kg N=62	Clobazam 1.0 mg/kg N=59
# patients with any	6.3% (2)	8.3% (3)	3.4% (2)	5.2% (3)	11.3% (7)	8.5% (5)

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SAEs						
Pneumonia	0	0	0	3.4% (2)	3.2% (2)	1.7% (1)
Constipation	0	2.8% (1)	0	0	1.6% (1)	1.7% (1)
Lobar pneumonia	0	0	1.7% (1)	0	0	3.4% (2)
Adverse drug reaction	0	0	0	1.7% (1)	0	0
Aspiration	0	2.8% (1)	0	0	0	0
Bronchopneumonia	0	0	0	0	0	1.7% (1)
Cyanosis	0	0	0	0	1.6% (1)	0
Depressed level of consciousness	0	0	0	0	0	1.7% (1)
Drug administration error	0	0	0	0	1.6% (1)	0
Drug toxicity	0	0	0	0	1.6% (1)	0
Grand mal convulsion	0	0	0	0	1.6% (1)	1.7% (1)
Headache	0	0	0	0	1.6% (1)	0
Influenza	0	0	0	0	0	1.7% (1)
Jaw fracture	0	0	1.7% (1)	0	0	0
Malnutrition	3.1% (1)	0	0	0	0	0
Metapneumovirus infection	0	0	0	1.7% (1)	0	0
Myoclonic epilepsy	0	0	0	0	1.6% (1)	0
Parainfluenza virus infection	0	0	0	0	0	1.7% (1)
Pyrexia	0	2.8% (1)	0	0	0	0
Respiratory distress	0	2.8% (1)	0	0	0	0
Respiratory failure	0	0	0	0	0	1.7% (1)
Rhinovirus infection	0	0	0	1.7% (1)	0	0
Sedation	0	0	0	1.7% (1)	0	0
Sleep apnea syndrome	3.1% (1)	0	0	0	0	0
Thrombocytopenia	0	0	0	0	1.6% (1)	0
Ultrasound abnormal	0	0	0	0	0	1.7% (1)
Vomiting	0	0	0	0	1.6% (1)	0

From 6/30/11 Submission, Table 6.2.1, pp. 807-810.

In the following paragraphs I summarize clinical details for select SAEs of special interest.

Adverse Drug Reaction

Subject 0058/7032 had a serious AE coded to the preferred term “Adverse drug reaction”. On study day 7, this 3 year old male experienced an erythematous rash on his chest, extremities, and chin, but no mucosal involvement. One lesion reportedly blistered. The patient was admitted to a hospital for 1 day and was treated with IV fluids, diphenhydramine, and cetirizine. The treating physician stopped the patient’s

lamotrigine and clobazam. The patient had been taking lamotrigine for approximately 7 months prior to the event. The rash was resolved on study day 12.

Drug toxicity

Subject 0822/7079, a 9-year-old Asian male with LGS, experienced a SAE that was coded to the preferred term “Drug toxicity”. The subject was randomized to 0.5mg/kg/day. During the titration phase, on Study Day 13, the subject received the study drug in the wrong sequence (i.e., in vertical row instead of horizontal row of blister card). The investigator did not document the number of tablets incorrectly administered. Subsequent to receiving the drug in the wrong sequence, the subject became restless and had imbalance. He was not able to walk properly and had a tendency to fall while walking. He also had extreme somnolence. The subject was hospitalized on Study Day 15 and the study drug regimen was immediately interrupted. The subject gradually improved over 2 days and the somnolence and restlessness reduced. The subject was discharged from the hospital on Study Day 18 and study drug was restarted on Study Day 19 with the morning dose.

Thrombocytopenia

Three subjects experienced four SAEs coded to the preferred term “thrombocytopenia”. The case narratives identified confounding factors for these events. One subject had a below normal platelet count at baseline, and her platelet count continued to decline during the trial. Thrombocytopenia (associated with macrocytic anemia) in the second patient was attributed to valproic acid and the patient’s platelet count improved after holding valproic acid for 3 doses and clobazam for 1 day. In the third case, the patient’s platelet count increased and decreased over the course of treatment with clobazam. I provide summaries for these events below.

Subject 0803/7132, a 2-year-old Asian female with LGS, was hospitalized for thrombocytopenia on Study Day 87. She developed pneumonia on Study Day 91 while hospitalized that the investigator considered medically important. Relevant medical history includes patent ductus arteriosus, vision impairment, hearing impairment, and delayed musculoskeletal and neurological development. No concomitant medications were recorded during the time of the events. Current AEDs included sodium valproate and phenytoin. The subject also experienced non-serious AEs of pyoderma, petechiae, lower respiratory tract infection, thrombocytopenia, and pyrexia during the trial. The subject’s platelet counts were below the normal range at screening (118 GI/L) and decreased to the lowest measured level of 13 GI/L on Study Day 87 per the central laboratory. Plasma valproic acid concentrations increased over this same time; on Study Day 52, her level of valproic acid was 726 umol/L (ULN=700 umol/L) and had increased to 938 umol/L on Study Day 88. The subject’s platelet counts and valproic acid concentrations during the trial are presented in the following table:

	Platelets (GI/L) normal range: 252-582	Valproic acid Concentration (umol/L)^a
Screening	118	672
Study Day 52	38	726
Study Day 81	26	794
Study Day 87*	13	--
Study Day 88	--	938
Study Day 89	26	--
Study Day 90	28	--

Study Day 91	20	--
Study Day 92	22	--
Study Day 96	125	--

a: therapeutic range 350-700 umol/L

--: not reported

*Day that clobazam and valproic acid were stopped

The subject was receiving a target dose of 0.5 mg/kg clobazam. Study drug and sodium valproate were both discontinued on Study Day 87 due to thrombocytopenia. She received 2 units of platelets on Study Day 88 and the thrombocytopenia resolved on Study Day 97. The Investigator considered the thrombocytopenia severe and possibly related to study drug. An alternative etiology of "due to valproic acid therapy and study drug" was recorded. The subject experienced a single episode of slight hemoptysis during hospitalization and a chest x-ray revealed ill-defined opacities in both upper lobes that were suggestive of pneumonitis. The subject was treated with amoxicillin with clavulanate potassium for the pneumonia. The pneumonia resolved on Study Day 119. The Investigator considered the pneumonia mild in severity and not related to study drug.

Subject 0008/0407, a 6-year-old white male with LGS, was hospitalized for pneumonia; enterocolitis; convulsion; talipes; and pyrexia and had a prolongation of hospitalization for macrocytic anaemia and thrombocytopenia during the trial. Relevant medical history included mentally challenged, tremors bilaterally, pneumonia, phenobarbital allergy, G-tube, and appendicitis. Concomitant medications recorded during the time of the events included ceftriaxone, salbutamol, paracetamol, azithromycin, famotidine, levocarnitine, cefdinir, metronidazole, calamine, antacids, ketorolac, ondansetron, fentanyl, dexamethasone, marcaine with epinephrine, midazolam, cefazolin, pethidine, morphine, unacid, and ibuprofen. AEDs administered during the trial included valproic acid, topiramate, fosphenytoin, lorazepam, levetiracetam, clonazepam, diazepam, and zonisamide. During the trial, the subject also had non-serious AEs of lethargy, asthenia, pneumonia (×4), dermatitis diaper, hallucination, talipes, and rash.

On Day 198, while receiving a TDD of 20 mg clobazam and being hospitalized for pneumonia, the subject experienced macrocytic anaemia (MCV of 105 fL, normal: 75-94 fL) and thrombocytopenia (platelet count of 65 x 10⁹, normal: 150-450 x 10⁹) that led to prolongation of hospitalization. On Day 199, the subject's platelet count was 57 x 10⁹ and a pediatric hematology consultation was obtained. The findings concluded that the changes in CBC indices were most likely valproic acid induced and, therefore, valproic acid dosing was held for 3 doses. Additionally, study drug dose was interrupted for 1 day and restarted at a TDD of 10 mg clobazam on Day 200. On Day 201, study drug dose was restarted at a TDD of 20 mg clobazam, adjusted on Days 202 and 204 due to hospital error, and adjusted on Day 205 to the correct TDD of 20 mg clobazam. The subject was discharged home on original valproic acid dose. These events resolved on Day 207.

Subject 0038/8002, an 11-year-old white female with LGS, was hospitalized for vomiting; convulsion and varicella; *klebsiella* cystitis; and pancreatic pseudocyst (x 2) during the trial. Several of these hospitalizations were associated with varying degrees of thrombocytopenia. Relevant medical history included infantile cerebral palsy, brain heterotopia, septo-optic dysplasia, cortical blindness, static encephalopathy, developmental delays, autism, mood lability, insomnia, nausea, dysmorphic features, problems with drooling and swallowing, occasional constipation, incontinent, spastic diplegia, contractures secondary to cerebral palsy, hypothyroid, panhypopituitarism, eczema, congenital factor VIII, von Willebrand's disease, obesity, multiple allergies, Schinzel-Giedion, nonconvulsive starring status epilepticus, and nausea. Concomitant medications recorded during the time of the events included hydrocortisone, escitalopram, macrogol, melatonin, multivitamins (plain), levothyroxine, cefotaxime, ondansetron, IV solutions, loratadine, cefprozil, fluconazole, nystatin, loratadine, EMLA cream, bacitracin,

paracetamol, ibuprofen, ceftriaxone, acyclovir, nitrofurantoin, mupirocin, ketorolac, enemas, methylprednisolone, lansoprazole, contrast media, clonidine, glucose, plasma, ampicillin, cefepime, morphine, *Lactobacillus acidophilus*, pantoprazole, solutions for parenteral nutrition, potassium, furosemide, piperacillin with tazobactam, gentamicin, midazolam, lactulose, albumin human, triamcinolone, desmopressin, meropenem, heparin, protein supplements, simethicone, and botulinum toxin type A. AEDs administered during the trial included carbamazepine, dexamethasone, valproic acid, levetiracetam, fosphenytoin, diazepam, and phenobarbital. On Day 628, while receiving a TDD of 20 mg clobazam, the subject experienced varicella, convulsions (exacerbations of seizures) and thrombocytopenia ($53 \times 10^9/L$, normal: $130\text{--}450 \times 10^9/L$) and was subsequently hospitalized and treated with ondansetron, EMLA cream, bacitracin cream, ibuprofen, ceftriaxone, IV solutions, paracetamol, acyclovir, levothyroxine, Lexapro, nitrofurantoin, loratadine, and mupirocin. The study drug dose was decreased to a TDD of 10 mg on Days 628 and 629 due to varicella and seizure exacerbation and was increased to a TDD of 20 mg on Day 630 to resume the normal dosing regimen. Seizures improved with the restart of clobazam. On Day 631, the subject's platelet count was $57 \times 10^9/L$. No platelet count was reported on the day of event resolution; however, the subject's platelet count was reported as $240 \times 10^9/L$ on Day 640. These events resolved on Day 632. The Investigator considered the AEs moderate in severity and not related to study drug.

On Day 655, while receiving a TDD of 20 mg clobazam, the subject experienced cystitis klebsiella and a second event of thrombocytopenia ($67 \times 10^9/L$) and was subsequently hospitalized and treated with ketorolac, ceftriaxone, nitrofurantoin, paracetamol, sodium chloride, cefprozil, IV solutions, dexamethasone, and lansoprazole. The study drug dose was increased to a TDD of 30 mg on Day 657 due to increased seizures, decreased to a TDD of 15 mg on Day 658 due to abdominal pain, and increased to a TDD of 30 mg on Day 659 to resume the normal dosing regimen. The events resolved on Day 665 (the subject's platelet count increased to $240 \times 10^9/L$ on Day 664). The Investigator considered the AE of cystitis klebsiella moderate in severity and the event of thrombocytopenia severe; both events were considered not related to study drug.

On Day 703, while receiving a TDD of 20 mg clobazam, the subject experienced pancreatic pseudocyst and a third event of thrombocytopenia ($105 \times 10^9/L$) and was subsequently hospitalized and treated with lansoprazole, glucose, paracetamol, ibuprofen, clonidine, phenobarbital, Desitin, ampicillin, cefepime, morphine, acyclovir, pantoprazole, nutritional supplements, *Lactobacillus acidophilus*, loratadine, furosemide, fluconazole, IV solutions, piperacillin/tazobactam, gentamicin, ampicillin, midazolam, mupirocin, plasma, and meropenem. Study drug dose was increased to at TDD of 30 mg on Day 712 due to increased seizures and then increased to a TDD of 45 mg on Day 733 due to increased seizures and valproic acid was discontinued due to the subject's platelet count ($58 \times 10^9/L$) on Day 706. The events resolved on Day 733 (the subject's platelet count was $238 \times 10^9/L$). The Investigator considered the AEs severe; the event of pancreatic pseudocyst was considered unlikely related to study drug and the event of thrombocytopenia was considered not related to study drug.

On Day 810, while receiving a TDD of 45 mg clobazam, the subject experienced a second event of pancreatic pseudocyst and was subsequently hospitalized and treated with nitrofurantoin, simethicone, and IV solutions. The study drug dose was increased to a TDD of 50 mg on Day 830, 70 mg on Day 885, and 75 mg on Day 941 due to increased seizures. The event was reported as ongoing as of the data cut off date for the trial. The Investigator considered the AE mild in severity and not related to study drug.

Pancreatitis

Two patients had SAEs of pancreatitis. According to the CRFs, both patients were taking valproic acid at the time of the pancreatitis AEs. In the first case, the event occurred in a patient who was hospitalized for septic shock secondary to gastrointestinal perforation and the event resolved without interruption of clobazam. The

second case occurred in a patient who was hospitalized for Guillain-Barre syndrome. I present information from the narratives for these events in the following paragraphs.

Subject 0003/0208, a 7-year-old (at the time of enrollment) white male with LGS, was hospitalized for aspiration pneumonia; septic shock secondary to gastrointestinal perforation; and pancreatitis during the trial. Relevant medical history included developmental delay, spastic quadriplegia, aspiration pneumonia, cortical visual impairment, hearing loss, increased upper airway secretions, cervical adenopathy, chronic respiratory infections, G-tube placed, intermittent constipation, ear infection, respiratory distress, cleft palate, ear tubes placed bilaterally, and right ear odor and drainage. Concomitant medications recorded during the time of the events included levocarnitine, pyridoxine, modafinil, dopamine, ceftriaxone, fentanyl, vancomycin, clindamycin, azithromycin, hydrocortisone, glycopyrronium, cefazolin, unacid, cefuroxime, multivitamin and mineral supplement, paracetamol, cefotaxime, metronidazole, ampicillin, dextrose and sodium chloride injection, and sodium chloride. Antiepileptic treatments administered during the trial included VNS, levetiracetam, valproic acid, and midazolam.

On Day 620, while receiving a TDD of 20 mg, the subject had the life-threatening events of septic shock, vomiting, and esophageal and gastric perforations post an elective hospitalization for a laparoscopic surgery for a hiatal hernia. The subject underwent successful surgery repair for the perforations. Study drug was temporarily interrupted but resumed on Day 621. The event of vomiting resolved on Day 620 and the events of gastrointestinal perforation resolved and septic shock resolved on Day 621. The Investigator considered the gastrointestinal perforation and septic shock severe and not related to study drug and the vomiting mild in severity and not related to study drug.

On Day 634, while hospitalized, the subject was diagnosed with pancreatitis and treated with cefotaxime, metronidazole, ampicillin, and IV fluids. He was receiving a TDD of 20 mg clobazam at the time of this event. Study drug dose remained unchanged. This event resolved on Day 652. The Investigator considered the AE moderate in severity and unlikely related to study drug.

Subject 0017/8102, a 11-year-old (at the time of enrollment) white male with LGS, was hospitalized for Guillain-Barre syndrome and pancreatitis during the trial. Relevant medical history included moderate cognitive impairment, mild left hemiparesis, slow and inaccurate, behavioral aggressive outburst, increased valproic serum levels, asthma, lung disease of prematurity, urinary incontinence, headaches, and mild circumduction left leg. Concomitant medications recorded during the time of the events included salbutamol, penicillin NOS, cefotaxime, diphenhydramine, immunoglobulin, paracetamol, rocuronium, atropine, chlorhexidine, fentanyl, midazolam, vancomycin, ibuprofen, furosemide, morphine, insulin aspart, insulin, potassium, glycopyrronium, oxacillin, ampicillin, pantoprazole, ranitidine, heparin, alteplase, bisacodyl, and macrogol. AEDs administered during the trial included topiramate, levetiracetam, and valproic acid. On Day 28, the subject experienced symptoms of increasing lethargy, weakness, and febrile illness, which led to hospitalization and diagnosis of Guillain-Barre syndrome. The subject was found to have increased CSF protein and an NCV and EMG consistent with Guillain-Barre syndrome. On Day 37, the subject developed mild abdominal discomfort, marked elevation of amylase and lipase, and was diagnosed with pancreatitis. He was treated with rocuronium, atropine, chlorhexidine, fentanyl, midazolam, salbutamol, cefotaxime, vancomycin, ibuprofen, furosemide, morphine, insulin aspart, insulin, potassium, glycopyrronium, oxacillin, ampicillin, pantoprazole, ranitidine, heparin, paracetamol, alteplase, bisacodyl, and macrogol. The subject had received placebo in Trial OV-1012 and was receiving a TDD of 20 mg clobazam at the time of these events. Study drug was interrupted on Day 28 due to the Guillain-Barre syndrome, restarted at a TDD of 10 mg on Day 29, interrupted on Day 30 due to the Guillain-Barre syndrome, and then restarted at a TDD of 10 mg on Day 51. The event of pancreatitis resolved on Day 71 and Guillain-Barre syndrome resolved on Day 72. The Investigator considered the both AEs severe and unlikely related to study drug.

Renal Tubular Necrosis

Subject 0012/7023, a 7-year-old male, experienced renal tubular necrosis while hospitalized for pneumonia and septic shock. These events resolved and the patient continued in the trial.

SAEs from Legacy Trials

In the Legacy epilepsy trial 301, 10% (12/119) of clobazam subjects and 32% (37/116) of control subjects experienced one or more SAEs. Convulsion (n=7) and Self injurious ideation (n=2) were the only SAEs reported by more than 1 clobazam subject in trial 301. The other SAEs reported for clobazam subjects were drug ineffective, pyrexia, gastroenteritis, pneumonia, diagnostic procedure, EEG, muscle twitching, muscular weakness, astrocytoma, complex partial seizures, dysarthria, facial paralysis, somnolence, status epilepticus, abnormal behavior, breathing related sleep disorder, depressed mood, depression, disturbance in social behavior, respiratory distress, sleep apnea, stridor, tonsillar hypertrophy, tendon transfer, and tonsillectomy (ISS, table 6.3.1).

In the Legacy psychiatry trials, 5/1,484 clobazam subjects had identified SAEs. The sponsor explained that a contributing factor for this small number of SAEs was that these trials were conducted in the 1970's, prior to the existence of a regulatory definition for SAEs. Therefore, SAEs were not prospectively reported in the legacy psychiatry trials (ISS, p.112). The sponsor identified the 5 SAEs noted above by reviewing CSR and CRFs for hospitalizations. Only 1 of the 5 SAEs was associated with an AE term in the database. Subject 0001-0004, a patient with anxiety, alcoholism, chronic bronchitis, and hypertension, experienced jaundice and admitted to drinking up to 2 quarts of beer per day. A liver biopsy was consistent with alcoholic cirrhosis. I provide the available details for this event below.

Subject 0001-0004 was a 47-year-old male with a history of alcoholism, chronic bronchitis, tobacco use, and hypertension who was hospitalized due to jaundice on Study Day 32 of a 5-week trial in anxious outpatients (4-week treatment period with 1-week dose deescalation). The subject's LFTs rose from Baseline (Day -4) to Day 14 as follows: total bilirubin 1.9 to 3.3 mg/100mL; alkaline phosphatase 230 to 550 U/L; and SGOT 400 to 720 U/L. At 4-weeks post-treatment, his LFTs were: total bilirubin 6.5 mg/100mL; alkaline phosphatase 470 U/L; and SGOT was 660 U/L. Physical examination revealed scleral icterus and palpable liver. Study medication was discontinued and he was hospitalized. A liver biopsy was consistent with alcoholic cirrhosis. The subject admitted drinking up to 2 quarts of beer per day during treatment. He had escalated to a TDD of clobazam 30 mg by the third week and was taking 20 mg/day at the time of the hospitalization.

The reasons for hospitalization for the remaining 4 patients were worsening of underlying psychiatric condition (n=2), appendicitis, and reason unknown.

7.3.3 Dropouts and/or Discontinuations

During the Phase I trials, 6.3% (n=22) of clobazam subjects discontinued prematurely. AE was the most common reason for discontinuation (3.7%, n= 13). The other reasons for discontinuation were withdrew consent (n=7), protocol violation (n=1), and other (n=1) (ISS table 12, p.64).

The adverse events leading to discontinuation during the Phase I trials were transaminase increased (n=3), delirium (n=3), somnolence (n=3), dizziness (n=2), depressed mood, libido decreased, erectile dysfunction, insomnia, dysarthria, gait disturbance, and mental status changes.

Two subjects with transaminase increases leading to discontinuation were from Phase I trial OV-1022 (40mg TDD) and one was from Phase I trial OV-1038 (30mg TDD). The subjects in trial OV-1022 experienced increases in both AST and ALT in the 120-230 U/L range and neither had increases in total bilirubin. The subject from OV-1038 experienced an increase in AST to 180 U/L and ALT 278 U/L and also did not experience an increase in total bilirubin. Transaminases returned to normal for all three subjects. Lundbeck's narrative summaries for these events are provided below.

Subject 1005, a 43-year-old white male of Hispanic/Latino ethnicity, entered the trial with no significant medical history. The subject completed the placebo and the clobazam 20 mg TDD dosing days with no reported adverse events. The subject began experiencing elevations in ALT on Day 14 (the 2nd day of 40 mg TDD dosing) and in AST on Day 17 (the 5th day of 40 mg TDD dosing) that continued throughout the dosing period. On Day 20, his ALT and AST concentrations were 203 U/L and 121 U/L, respectively, and the subject was withdrawn from the trial. These elevations were not accompanied by increases in direct or total bilirubin. Following study drug discontinuation, the ALT and AST began to decrease and were within the normal range approximately 2 weeks later. The investigator considered these elevations to be probably attributable to clobazam dosing. This subject also developed mild oropharyngeal pain approximately 1 week after study drug discontinuation. The investigator considered this to be related to viral pharyngitis and not to the study drug.

Subject 1050, a 45-year-old white female of Hispanic/Latino ethnicity, entered the trial with a medical history of contact dermatitis, presbyopia, bilateral salpingo-oophorectomy, hysterectomy, and mammoplasty breast reduction. On Day 10 (20 mg TDD), the subject experienced moderate constipation that the investigator considered to have a possible alternate etiology of dietary changes, and the subject was treated with prune juice, glycerin suppository, and milk of magnesia. The subject began experiencing elevations in ALT and AST on Day 14 (the 2nd day of 40 mg TDD dosing) that continued to increase, and on Day 16 (40 mg TDD) were 212 U/L and 198 U/L, respectively. Alkaline phosphatase was also elevated on Day 16 (191 U/L) and Day 17 (230 U/L). The subject was withdrawn from the trial following the morning dose on Day 16, and the ALT/AST concentrations continued to remain elevated over the next 2 days, and then decreased to the normal range approximately 10 days after study drug discontinuation. The elevations in ALT/AST were not accompanied by increases in direct or total bilirubin. The investigator considered these elevations to have a possible alternate etiology of diet.

Subject 2008, a 36-year old woman with a medical history of Caesarian-section, saline breast augmentation, and bilateral tubal ligation, experienced increased transaminases on Day 3 of the 30 mg/day dose. The subject had received a total of 9 days of study drug. On Day 3 of the 30 mg/day dose (Study Day 9), the ALT was 151 U/L (ULN=40 U/L) and the

AST was 180 U/L (ULN 30 U/L). Study drug was discontinued. The maximum ALT of 278 U/L and AST of 180 U/L were reported on Study Day 10. The transaminase levels began to decline and were within normal limits on Study Day 23. Bilirubin levels remained within normal limits throughout the trial. The investigator considered that increased transaminases moderate in intensity and probably related to study drug.

Phase II/III Trials

During trial OV-1002, 10 clobazam subjects withdrew prematurely. In trial OV-1012, 43 clobazam and 18 placebo subjects withdrew prematurely. In trial OV-1002, AE was the most common reason for premature discontinuation (n=7), followed by withdrew consent (n=2) and other (n=1). In trial OV-1012, AE was also the most common reason for premature discontinuation for clobazam subjects (n=24), followed by withdrew consent (n=5), lack of efficacy (n=5) lost to follow up (n=4), protocol violation (n=3) and other (n=2). The reasons for premature discontinuation for placebo subjects in OV-1012 were lack of efficacy (n=10), withdrew consent (n=4), AE (n=2) and lost to follow up (n=2) (ISS table 13, p.65). Through the 120 day safety update, 60 subjects prematurely discontinued from trial OV-1004. The reasons for discontinuation were subject/caregiver/parent request (8.2%, n=22), lack of efficacy (5.2%, n=14), AE (3.4%, n=9), death (2.6%, n=7), other (1.1%, n=3), and protocol violation (0.4%, n=1) (120 Day Safety Update Table 2, p.16).

In all three clobazam phase II/III LGS trials, 16% (46/300) of patients had one or more AEs that led to discontinuation. The AEs leading to discontinuation of more than one patient were somnolence (n=7), aggression (n=6), lethargy (n=5), ataxia (n=4), pneumonia (n=3), death (n=2), fatigue (n=2), insomnia (n=2), restlessness (n=2), and urinary incontinence (n=2). The AEs leading to discontinuation of 1 patient each were thrombocytopenia, supraventricular tachycardia, dysphagia, fecal incontinence, salivary hypersecretion, adverse drug reaction, chest pain, gait disturbance, irritability, sepsis, urinary tract infection, drug toxicity, hyperammonemia, hypophagia, chorea, cognitive disorder, convulsion, drooling, epilepsy, hypotonia, motor dysfunction, sedation, abnormal behavior, binge eating, listless, negativism, perseveration, acute respiratory distress syndrome, atelectasis, increased bronchial secretion, respiratory failure, and rash (120 Safety Update, Table 7.2.4, pp. 3461-5).

In the 2 controlled phase II/III clobazam LGS trials, overall discontinuations due to AEs suggested a dose response. In trial OV-1002, 9.5% (3/32) of low dose clobazam patients discontinued for AEs compared to 11.1% (4/36) of high dose patients. In trial OV-1012, 3.4% (2/59) of placebo patients discontinued for AEs compared to 6.9% (4/58) of clobazam low dose, 12.9% (8/62) of clobazam medium dose and 22% (13/59) of clobazam high dose patients. In the following table, I identify the AEs leading to discontinuation that occurred more frequently in higher dose groups compared to low dose groups. In general, the small number of events does not provide robust evidence of dose response for any particular AE leading to discontinuation.

AEs leading to discontinuation that occurred more frequently among higher dose groups, from double blind phase II/III trials OV-1002, OV-1012

AE	Trial OV-1002		Trial OV-1012			
	Clobazam 0.25mg/kg N=32	Clobazam 1.0 mg/kg N=36	Placebo N=59	Clobazam 0.25mg/kg N=58	Clobazam 0.50mg/kg N=62	Clobazam 1.0 mg/kg N=59
# patients with any AEs leading to discontinuation	9.4% (3)	11.1% (4)	3.4% (2)	6.9% (4)	12.9% (8)	22% (13)
Fecal incontinence	0	2.8% (1)	0	0	0	0
Fatigue	0	0	0	0	0	3.4% (2)
Gait disturbance	0	0	0	0	0	1.7% (1)
Irritability	0	0	0	0	1.6% (1)	0
Urinary tract infection	0	0	0	0	1.6% (1)	0
Ataxia	0	0	0	0	0	6.8% (4)
Chorea	0	2.8% (1)	0	0	0	0
Droling	0	0	0	0	0	1.7% (1)
Hypotonia	0	0	0	0	0	1.7% (1)
Lethargy	0	0	1.7% (1)	1.7% (1)	1.6% (1)	5.1% (3)
Motor dysfunction	0	0	0	0	0	1.7% (1)
Sedation	0	0	0	0	0	1.7% (1)
Somnolence	0	2.8% (1)	0	0	3.2% (2)	5.1% (3)
Abnormal behavior	0	2.8% (1)	0	0	0	0
Aggression	3.1% (1)	0	0	0	1.6% (1)	5.1% (3)
Binge eating	0	0	0	0	0	1.7% (1)
Insomnia	0	0	0	0	1.6% (1)	1.7% (1)
Listless	0	0	0	0	0	1.7% (1)
Negativism	0	2.8% (1)	0	0	0	0
Perseveration	0	0	0	0	0	1.7% (1)
Restlessness	0	0	0	0	1.6% (1)	0
Urinary incontinence	0	2.8% (1)	0	0	1.6% (1)	0

From ISS Table 7.2.1, pp. 4224-4228.

Below, I summarize information for the patient who discontinued for rash.

Subject 0017/7005, a 2 year old male with a history of macrocephaly, mild mental retardation, infantile spasms, visual changes possibly due to vigabatrin, nonverbal, rhabdomyomas, pyloric stenosis, mild left hydronephrosis, renal lipomatosis, tuberous sclerosis, depigmented macules, upper respiratory infection fever, and diarrhea discontinued from trial 1004 for rash. Concomitant medications were amoxicillin, paracetamol, diphenhydramine, and ibuprofen and AEDs were topiramate, levetiracetam, and valproic acid. On Day 11, the subject experienced a mild rash (event diagnosis febrile exanthema). On Day 13, an additional event of severe rash was reported; however, the mild rash continued. The mild rash was associated with a palpable spleen tip, granulocytopenia, sedimentation rate elevated, anemia, otitis media, liver enzyme elevation, and fever. The subject was treated with amoxicillin, paracetamol, ibuprofen, diphenhydramine, prednisolone, and albuterol. On Day 1, the subject's AST (28 U/L, normal range: 15-60 U/L) and ALT (15 U/L, normal range: 3-35 U/L) were within normal range; hematocrit data were unavailable. On Day 16, per the site local laboratory, the subject's AST, ALT, were above normal range (365 U/L, 351 U/L, respectively) and hematocrit was 29.5%, [normal range: 31.0- 41.0%]. Central

laboratory results for Day 1, Day 38, and Day 66 (early termination visit) AST and ALT were within normal range. Study drug was prematurely discontinued on Day 17. The mild rash resolved on Day 28 and the severe rash resolved on Day 66. The Investigator considered the first event of rash mild and possibly related to study drug and the second event of rash severe and probably related to study drug. In light of the fact that the subject had rash, fever, and internal organ involvement (splenomegaly), the event was reviewed as a possible case of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), but was deemed not to fit the definition. This case is discussed in greater detail below, in the review of DRESS.

In the legacy epilepsy trial (301), 10.9% (13/119) of clobazam patients and 29.3% (34/116) of active control patients discontinued for AEs. The AEs reported for the clobazam subjects who discontinued prematurely were abnormal behavior (n=3), drug ineffective (n=3), irritability (n=2), weight increased (n=2), abdominal pain, abdominal pain upper, aggression, appendicitis, balance disorder, convulsion, coordination abnormal, depression, disturbance in attention, drooling, fatigue, headache, hypersomnia, inappropriate affect, lethargy, nausea, personality change, psychomotor hyperactivity, poor quality sleep, rash, retching, somnolence, and vomiting (ISS Table 51, pp.122-123).

Lundbeck also commented on withdrawals due to an event labeled “catastrophic personality disintegration” or CPD. Specifically, the sponsor noted that in Trial 301, 3 clobazam subjects (Subjects 0006-0007, 0013-0068, and 0013-0077), 3 carbamazepine subjects, and one phenytoin subject discontinued for CPD. CPD was collected separately from AEs in this trial. The sponsor explained that CPD has only been described once in the literature. The CPD constellation of symptoms was originally observed in a study by Sheth, Goulden, and Ronen (one of the investigators participating in the Legacy Epilepsy Trial 301) in 1994. In the published results of this study, CPD was characterized by aggressive agitation, self-injurious behavior, insomnia, and incessant motor activity occurring in 7 children (6 on multiple AEDs, one receiving clobazam monotherapy). The affected children were relatively young (mean age 6.4 years) and developmentally disabled (4 were autistic and 2 had isolated mental retardation). The behavioral deterioration resolved after clobazam was discontinued. The sponsor felt that the reason CPD was singled out in Legacy Epilepsy Trial 301 was due to the previous experience of Dr. Ronen (ISS, p. 124).

Lundbeck presented the AE resulting in withdrawal data from legacy psychiatry trials in 4 separate tables. Lundbeck used their groupings of legacy psychiatry trials (described above) to present these data. Below, I summarize the AEs leading to withdrawal that occurred in at least 2 clobazam patients and that occurred more frequently compare to placebo.

Discontinuations due to AEs that occurred in at least 2 clobazam subjects and that occurred more frequently compared to placebo, Legacy Psychiatry Trials By Analysis Group

AE leading to discontinuation	Treatment		
	Placebo (n=68)	Clobazam (n=203)	Diazepam (n=133)
Controlled Legacy Psychiatry Trials, US and Canada			
Any	4.4% (3)	8.9% (18)	11.3% (15)
Somnolence	0	3% (6)	3% (4)
Confusional state	0	1% (2)	0.8% (1)
Depression	0	1% (2)	1.5% (2)
Controlled Legacy Psychiatry Trials, Rest of the World			
Any	3.7% (7)	2.5% (10)	1.6% (4)
Controlled Legacy Psychiatry Trials, non-CRF			
Any	5.5% (20)	7.2% (44)	7.1% (32)
Asthenia	0.3% (1)	0.7% (4)	0
Fatigue	0.3% (1)	0.5% (3)	0.2% (1)
Irritability	0.3% (1)	0.7% (4)	0.4% (2)
Somnolence	0.3% (1)	1.5% (9)	1.8% (8)
Syncope	0	0.3% (2)	0.4% (2)
Depression	0.5% (2)	0.7% (4)	0.4% (2)
Erectile dysfunction	0	0.3% (2)	0.4% (2)
Urticaria	0	0.3% (2)	0

Note: No patients were recorded as discontinuing from the Uncontrolled Legacy Trials with CRFs.

No patients in the legacy Psychiatry trials discontinued for AEs of pancreatitis, acute renal failure, Stevens Johnson syndrome, toxic epidermal necrolysis, acute liver failure, transaminase elevations, rhabdomyolysis, aplastic anemia, agranulocytosis or thrombocytopenia.

In addition to the patients listed above, Lundbeck identified 30 patients who had “adverse event” listed as the reason for discontinuation (under disposition) but did not have a corresponding AE term identified for the event (ISS, Table 52, pp. 126-127). Current medical condition or illness was reported as the reason for discontinuation for 16 of these subjects. Six subjects apparently discontinued for side effects but no side effects were identified in the study reports for these subjects. The remaining reasons for discontinuation included worsening underlying psychiatric condition, hospitalization for unknown reason, appendicitis, upper respiratory infection, vomiting, failing to return and hospitalization, therapeutic abortion, and enuresis.

7.3.4 Significant Adverse Events

Lundbeck further explored the safety database for evidence of causal association between clobazam and a list of specific AEs. Lundbeck created the list of AEs for further evaluation by considering the characteristics of the intended treatment population, and the AEs associated with the use of other AEDs. The specific AEs that Lundbeck evaluated were AEs related to seizures (status epilepticus, new seizure types, and exacerbation of pre-existing seizure), pneumonia, blood dyscrasias, serious skin reactions, liver injury, cancer, suicidality, sudden unexplained death in epilepsy (SUDEP), and drug rash with eosinophilia and systemic symptoms (DRESS) (Summary of Clinical Safety, p.54).

Seizure-related AEs

Lundbeck did not find strong evidence to support that clobazam increased the risk of developing a new seizure type. In trial OV-1012 the risk of developing a new seizure type was 3.4% (2/59) in the placebo group and 3.4% (6/179) in the clobazam group (low dose 1.7%, 1/58; medium dose 3.2%, 2/62; high dose 5%, 3/59). In trial OV-1002, 3.1% (1/32) of low dose patients and 8.3% (3/36) of high dose patients developed a new seizure type during the trial. During the open label extension trial OV-1004, 7% (19/267) of patients developed a new seizure type (120 day Safety Update, p.36).

Lundbeck did not find strong evidence to support that clobazam was associated with increased seizure frequency. Lundbeck looked for evidence of increased seizure frequency with clobazam by examining AEs and analyzing seizure diaries.

No status epilepticus AEs were reported during OV-1012. Two patients in trial OV-1012 were hospitalized for seizure exacerbation. In both cases, the seizures resolved and the patients completed trial OV-1012 and enrolled in the open label extension trial OV-1004. No patients from OV-1012 discontinued for exacerbation of seizures. Seizure diary data showed that the frequency of drop or non-drop seizures was lower in clobazam patients compared to placebo. Forty-seven percent (27/57) of the placebo group showed worsening of average weekly seizure frequency (maintenance vs. baseline), compared to 32% (17/53) of the low dose clobazam group, 24% (14/58) of the medium dose clobazam group, and 12.2%, (6/49) of the high dose clobazam group (ISS, Table 54, p.131).

No status epilepticus AEs were reported during OV-1002. No patients were hospitalized for increased seizure frequency but 2 patients discontinued for seizure exacerbation AEs. When comparing maintenance phase to baseline, 22% (7/32) of low dose and no high dose patients (0/36) experienced an increase in drop seizures. In addition, 25% (8/32) low dose and 11% (4/36) of high dose patients experienced an increase in non-drop seizures (ISS, p.133).

Thirty-six patients in open-label extension trial OV-1004 had one or more seizure exacerbation AE (one SAE). One subject discontinued from 1004 for a seizure

exacerbation AE. Eight patients in OV-1004 had a status epilepticus AE (120 day Safety Update, pp. 38-39).

Safety data from legacy epilepsy trial (301) did not suggest that clobazam was associated with a higher risk for development of new seizure type or increase in seizure frequency when compared to active controls (phenytoin, carbamazepine). No new seizure types were reported in this trial. One clobazam patient (1/119) and one active control patient (1/116) experienced a status epilepticus SAE. There were 8 SAEs related to seizure among clobazam subjects (7 convulsion, 1 complex partial seizure) compared to 7 among active control patients (5 convulsion, 1 grand mal convulsion, 1 partial seizure).

Pneumonia

Lundbeck provided a summary of the number of pneumonia AEs with clobazam. Lundbeck searched for pneumonia-related AEs using an extensive list of over 50 AE terms for pneumonia (ISS Table 7.6.1.1). Lundbeck reported that there were no pneumonia-related AEs in the Phase I trials or the Legacy Psychiatry trials and one pneumonia-related AE in the Legacy epilepsy trial. The risk for all pneumonia-related AEs in clobazam patients in the LGS RCTs was 4% (10/247). In RCT OV-1002, there were 2 non-serious pneumonia-related AEs (both high dose). In RCT OV-1012, there were 8 pneumonia-related AEs (4.5%, 8/179) in patients taking clobazam (all SAEs, 2 low dose, 2 medium dose, and 4 high dose). In this trial, 1 placebo patient experienced a pneumonia-related SAE (1.7%, 1/59). In trial OV-1004, the open label extension trial, 46 patients experienced one or more pneumonia-related AEs (15%, 46/300) (120 day Safety Update, p.39).

(b) (4)

(b) (4)

The Division requested additional analyses of pneumonia-related AEs in clobazam patients. Specifically, the Division requested an evaluation of time to event and exploration of the data for predictive factors for pneumonia including demographic factors, clobazam dose, clobazam dose increases, history of pneumonia, history of aspiration, and history of swallowing difficulties. We also asked Lundbeck to evaluate whether factors they identify

(b) (4)

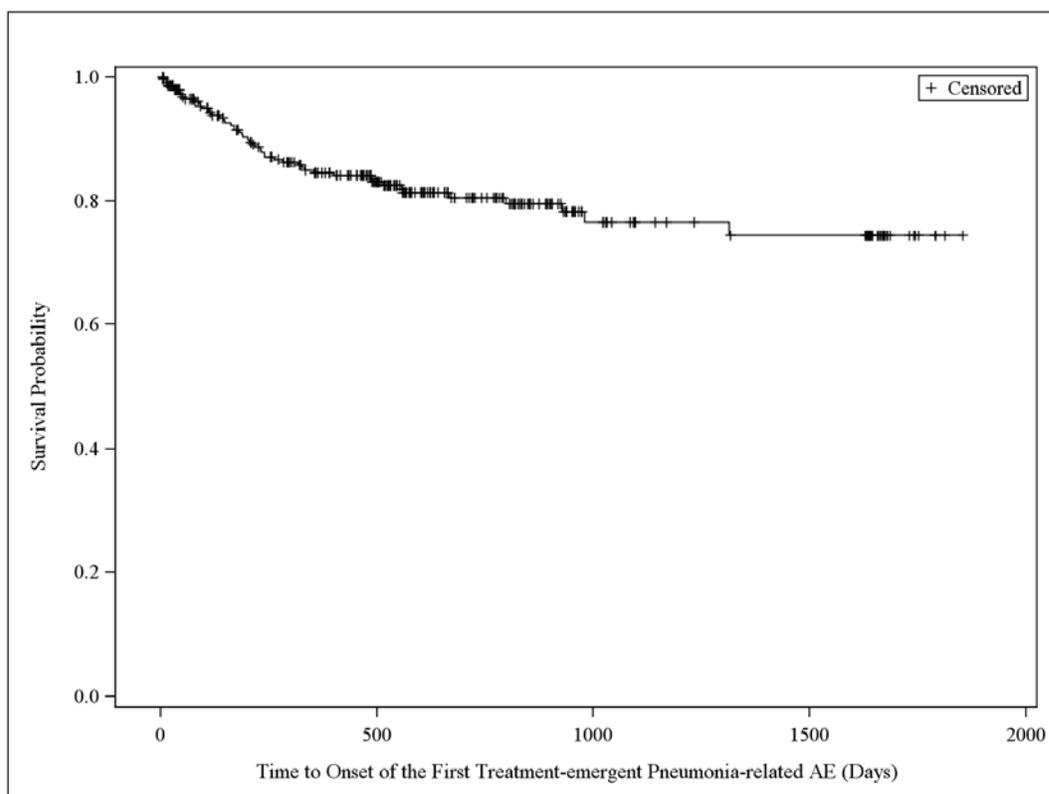
Specifically, the Division requested that Lundbeck determine if patients who experienced somnolence-related AEs (see above) or increased secretions/drooling AEs were at increased risk for developing pneumonia. The Division also asked Lundbeck to identify the pneumonia

cases that were temporally related to seizures. Lundbeck provided their responses in a 6/17/11 submission.

Time to onset

Lundbeck reported that the time to onset for pneumonia AEs in the Phase II/III trials ranged from 5-1853 days. The following graph displays time to onset for clobazam pneumonia cases.

*Figure 3
Time to Onset of the First Treatment-emergent Pneumonia-related Adverse Event During All Clobazam Treatment in Phase 2/3 LGS Studies
Safety Population*



The pneumonia AE risk appeared fairly constant through the first 500 days of treatment with a plateau in the survival curve after that time period.

Pneumonia Predictive Covariates

Using logistic regression analysis, Lundbeck attempted to identify covariates that predicted pneumonia events in clobazam treated patients. Lundbeck considered a number of covariates including age, sex, ethnicity, race, region of trial site, treatment (clobazam low, medium, or high dose), concomitant use of other specific medications and classes of medications, history of pneumonia, history of aspiration, history of dysphagia/GE-reflux/feeding tube placement, history of drooling/hypersecretion, AE of drooling/hypersecretion prior to pneumonia, somnolence-related AE prior to

pneumonia, AE within HLT of upper respiratory infection prior to pneumonia, and AE within HLT lower respiratory infection prior to pneumonia.

In their 7/29/11 submission, Lundbeck reported that younger age, use of Felbamate and use of an opioid were predictive for pneumonia but that use of rufinamide was protective. Lundbeck also noted that there did not appear to be an imbalance of these covariates at baseline for the different treatment groups in OV-1012.

Relationship between Pneumonia and other AEs

Lundbeck provided the number of pneumonia-related AEs that also had a somnolence-related AE, and separately, a drooling or salivary hypersecretion AE, in the 14 days prior to the pneumonia event. In addition, Lundbeck reviewed the seizure logs from the controlled Phase II/III trials to explore the relationship between seizure and pneumonia AEs. Lundbeck was not able to provide a similar analysis from the open label trial because the protocol for the open label trial required that seizures only be recorded in the 7 days prior to a trial visit.

Consistent with the regression analysis findings, Lundbeck's AE analysis found that somnolence related AEs, and drooling/salivary hypersecretion AEs did not commonly precede pneumonia AEs. Lundbeck reported that for approximately 7% of the pneumonia AEs (7/106), occurred in patients with a somnolence-related AE in the 14 days preceding the pneumonia. One of the pneumonia AEs (0.9%, 1/106) occurred in a patient with a drooling/salivary hypersecretion AE in the 14 days preceding the pneumonia.

For the 10 pneumonia events in the controlled clobazam trials, Lundbeck found that 8 occurred in patients who experienced a seizure in the preceding 5 days. Lundbeck acknowledged that the small numbers of events preclude any firm conclusions about the contribution of seizures to the risk for pneumonia in these patients.

Relationship between Pneumonia and Clobazam Dose Increases

To better understand the relationship between clobazam dose increases and pneumonia-related events, Lundbeck identified the number of pneumonia-related events where there was also a clobazam dose increase in the 7 days prior to the pneumonia-related AE. Lundbeck found that clobazam dose increases did not commonly precede pneumonia-related AEs. Lundbeck reported that approximately 7% (7/106) of the pneumonia-related AEs occurred in patients who had a clobazam dose increase in the 7 days prior to the pneumonia AE.

Post Marketing Pneumonia Reports

In addition to the available clinical trial data, Lundbeck summarized the post marketing adverse event report data for pneumonia (see below). Lundbeck found 23 post marketing reports of pneumonia with clobazam. Many of these reports documented that the patients had underlying risk factors for pneumonia.

Pneumonia AEs with other Approved LGS AEDs

Pneumonia AEs were also observed in LGS trials for other approved AEDs. To examine pneumonia risk in LGS AED programs, I reviewed available information for FDA approved for LGS drugs (clonazepam, felbamate, lamotrigine, topiramate, and rufinamide). The labels for clonazepam and lamotrigine do not provide separate AE data for LGS trials. In the felbamate label, in their LGS trial that included 31 felbamate and 27 placebo subjects, pneumonia did not meet the criteria for inclusion in the AE table (>1 subject). In the topiramate sNDA medical review dated 5/9/98, in LGS trial YL, 2/50 (4%) of topiramate subjects (subjects 29 and 49) had SAEs of pneumonia. The rufinamide NDA submission included data from one LGS RCT (0022) and an extension trial (0022E). In the RCT, 2 rufinamide (2.7%, 2/74) and no placebo patients (0/64) had AEs of pneumonia (Study report 0022, Post text table 10.1-2). The sponsor reported that for the rufinamide treated patients in the RCT and in the open label extension, the pneumonia AE risk was 8.1% (11/135) (NDA 021-911, Appendix 1, Post text table 6.8.1-2).

Literature Search for Pneumonia with Clobazam, Benzodiazepines

I searched PubMed for publications reporting a relationship between clobazam and pneumonia or benzodiazepines and pneumonia. I found no publications using the search terms “pneumonia” and “clobazam”. The search terms “benzodiazepine” and “pneumonia” returned a number of publications but none suggesting a link between benzodiazepine use and increased risk of developing pneumonia.

Discussion

Although pneumonia occurred commonly in LGS patients in the clobazam development program, there is insufficient evidence to determine if there is a causal relationship with clobazam. As noted above, the clobazam LGS development program included only 1 randomized, placebo-controlled trial. While there was an increase in pneumonia related AEs with clobazam compared to placebo in OV-1012, this finding is based on a relatively small number of events.

Another complicating factor in assessing the pneumonia risk with clobazam is that LGS patients have an increased risk for pneumonia, meaning that pneumonia is an expected event in the background for this population. The pre-trial medical history for many of these LGS patients included episodes of pneumonia and aspiration. Seizures, the treatment indication, increase pneumonia risk. Many of these patients also have feedings tubes that could increase the risk for aspiration and pneumonia. As noted above, pneumonia AEs were also observed in the LGS patients in the topiramate and rufinamide trials. Furthermore, Lundbeck reported that pneumonia was not observed in the clobazam patients in the Phase I trials or the Legacy Psychiatry trials, and that pneumonia risk was much less common in pediatric clobazam patients in the Legacy epilepsy trial.

Additional post-hoc analyses did not appear to provide convincing supportive evidence of an association between pneumonia and clobazam. Lundbeck's analyses did not find that clobazam dose or clobazam dose increases were associated with pneumonia AEs. Somnolence-related AEs and increased secretions, known side effects of clobazam, also did not appear to be related to pneumonia risk. Analyses did find that younger age, use of Felbamate, and use of an opioid was predictive for pneumonia-related AEs and that RCT patients with pneumonia-related AEs were likely to have had a seizure preceding pneumonia.

Given the findings from a single RCT, the non-supporting findings from the post hoc analyses, the lack of evidence in the medical literature and the relatively small number of pneumonia post marketing reports, the evidence suggests that the observed pneumonia cases are most likely related to underlying risk factors in the treated population. The available data are not sufficient to completely exclude the possibility that clobazam contributed to the risk for pneumonia events in the LGS population.

Blood dyscrasias

Lundbeck noted that no patients experienced a blood dyscrasia related AE in Phase I trials, the legacy Epilepsy trial, or the legacy Psychiatry trials. Eighteen clobazam patients experienced one or more blood dyscrasia AEs in trials OV-1002 (n=0), OV-1012 (n=4), and OV-1004 (n=15). One patient (0803-7115) had a low platelet AE in trial OV-1012 and again in trial OV-1004. Of the 18 patients with a blood dyscrasia AE, 16 experienced low platelet counts, 1 had a red blood cell count decrease AE, and 1 had a leucopenia AE.

Lundbeck noted that 3 patients experienced one or more thrombocytopenia SAEs. One of these patients was also taking valproic acid, one was also taking phenytoin and valproic acid and one was also taking carbamazepine and valproic acid. Lundbeck noted that each of these concomitant AEDs have been associated with thrombocytopenia.

For the patients with non-serious thrombocytopenia AEs, Lundbeck reported that all were taking either valproic acid and or carbamazepine at the time of the event.

Serious Skin Reactions

Lundbeck found no cases of serious skin reactions in the clobazam clinical trials safety databases. Lundbeck used the following list of AE terms for their search: Acute generalised exanthematous pustulosis, Cutaneous vasculitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalized, Epidermal necrosis, Erythema multiforme, Exfoliative rash, Skin necrosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, and Toxic skin eruption. Above, I provided a summary of an AE of rash that led to discontinuation. In addition, one serious AE that was a hospitalization for a rash was coded to the preferred term adverse drug reaction (see above).

Drug Induced Liver Injury

Lundbeck assessed the potential for drug induced liver injury with clobazam by reviewing lab data results and liver-related AE risks from clobazam clinical trials.

In Phase I trials, the risk for liver related lab result elevations was similar for subjects receiving clobazam and those receiving placebo or active control. There were no cases where subjects had transaminase elevations greater than or equal to 3x upper limit of normal (ULN) associated with total bilirubin $\geq 1.5 \times \text{ULN}$. The following table summarizes the liver related lab test outlier results for the Phase I trials.

Liver lab test result outliers, Clobazam Phase I Trials

Test/Cutoff threshold	Placebo/Positive Control N=140	Clobazam N=349
Aminotransferase>ULN	9.3% (13)	12.6% (44)
Aminotransferase $\geq 3 \times \text{ULN}$	1.4% (2)	2.3% (8)
Aminotransferase $\geq 5 \times \text{ULN}$	0	0.9% (3)
Total bilirubin >ULN	2.9% (4)	2% (7)
Total bilirubin $\geq 2 \times \text{ULN}$	0	0
ALP $\geq 1.5 \times \text{ULN}$	0	0.3% (1)

No subjects had transaminase elevations $\geq 10 \times \text{ULN}$
From ISS Table 8.1.1.2, p.5148-5149

The limited available data from the phase II/III trials did not suggest an increased risk for liver related lab test elevations for clobazam patients. There were no cases where subjects had transaminase elevations greater than or equal to 3x ULN associated with total bilirubin $\geq 1.5 \times \text{ULN}$. The following table summarizes the liver related lab test outlier results for the Phase II/III trials.

Liver lab test result outliers, Clobazam Phase II/III Trials

Test/Cutoff threshold	OV-1002		OV-1012			
	Clobazam 0.25mg/kg N=32	Clobazam 1.0mg/kg N=32	Placebo N=59	Clobazam 0.25mg/kg N=58	Clobazam 0.5mg/kg N=62	Clobazam 1.0mg/kg N=59
AT>ULN	15.6% (5)	16.7% (6)	11.9% (7)	12.1% (7)	9.7% (6)	20.3% (12)
AT $\geq 3 \times \text{ULN}$	3.1% (1)	2.8% (1)	1.7% (1)	0	0	0
AT $\geq 5 \times \text{ULN}$	0	2.8% (1)	1.7% (1)	0	0	0
Total bilirubin>ULN	0	0	1.7% (1)	0	0	0
ALP $\geq 1.5 \times \text{ULN}$	0	0	1.7% (1)	0	0	1.7% (1)

No clobazam subjects had transaminase elevations $\geq 10 \times \text{ULN}$
From ISS table 8.2.1.3.2, pp. 5288-5289

In the open label extension trial OV-1004, 1.5% (n=4) of subjects experienced a transaminase elevation \geq to 3x ULN and 0.7% (n=2) experienced a transaminase elevation $\geq 5 \times \text{ULN}$. No subjects experienced a transaminase elevation $\geq 10 \times \text{ULN}$. No subjects in OV-1004 experienced a total bilirubin >ULN (ISS table 8.2.1.6.2, p.5304).

No subjects in the legacy epilepsy trial had a transaminase elevation $\geq 3xULN$ and no subjects had a total bilirubin result that was greater than or equal to ULN.

No subjects in the US and Canadian legacy Psychiatry trials had a transaminase elevation $\geq 3xULN$. No placebo subjects (0/51), 1 clobazam subject (1/109) and 1 diazepam subject (1/54) experienced a total bilirubin $\geq 2xULN$ (ISS table 8.2.1.14.5, p. 5530).

In addition to summarizing liver-related lab data, Lundbeck also summarized liver-related AE risks from clobazam trials. In phase I trials, 7 (2%, 7/349) clobazam subjects had a liver-related AE (transaminase elevated $n=6$, alanine aminotransferase elevated). In those same trials, 2 comparator subjects (1.4%, 2/140) had liver-related AEs (1 placebo, 1 active control, both with transaminase elevated).

In trial OV-1012, 1 placebo patient and 1 clobazam (low dose) patient experienced a liver-related AE. In OV-1002, 2 high dose clobazam subjects experienced a liver-related AE. The liver-related AEs in clobazam patients were hepatic enzyme increased, alanine aminotransferase and aspartate aminotransferase increased, and blood alkaline phosphatase increased. These AEs were considered mild and did not lead to discontinuation.

In open label extension trial OV-1004, 9 subjects had liver related AEs (elevated LFTs $n=7$, alkaline phosphatase increased $n=2$), one of which was serious. That event is summarized below.

Subject 0017-7028, a 5-year-old female with LGS, experienced a non-serious AE of hepatic enzyme increased on Day 478 and a serious AE of hepatic enzyme increased on Day 855. Relevant medical history included microcephaly, spastic profound mental retardation with cerebral palsy, profound cognitive impairment, quadriplegia, unable to sit or reach, non-ambulatory, cannot stand, tracheomalacia, right microphthalmia, slowly reactive pupils, tracheostomy, gum hyperplasia, chronic congestion, G-tube, Nissen fundoplication, ankle contractures, Dandy Walker malformation, diffuse hyperreflexia, ankleclonus, and positive babinski responses. Concomitant medications recorded during the time of the event included ciprofloxacin and azithromycin. AEDs administered during the trial included phenobarbital, topiramate, and diazepam. The subject had received 106 days of clobazam at a target dose of 1.0 mg/kg in Trial OV-1012 and was receiving a TDD of 10 mg clobazam at the time of the first event. The subject had elevated ALT values on Day 478 ($6.14 \times ULN$), which peaked on Day 485 ($9.88 \times ULN$), and were still elevated on Day 660 ($5.61 \times ULN$). She also had elevated AST values: $2.08 \times ULN$ on Day 478; $5.47 \times ULN$ on Day 485; and $2.00 \times ULN$ on Day 660. Total bilirubin values were normal throughout the trial. On Day 885, the subject was hospitalized for further evaluation of hepatic enzyme increased and possible liver biopsy. The patient was receiving a TDD of 15 mg clobazam at the time of this event. An abdominal ultrasound showed evidence of cholelithiasis and small gall stones, but no irregularities in the liver. A liver biopsy was performed and the report included mild hydropic changes of hepatocytes and minimal lymphocytic infiltrate in one portal triad; no definite evidence of toxic hepatitis, viral inclusions, PAS+, diastase resistant granules seen by special stain was identified. No evidence of stainable iron seen by special stain. The subject had elevated ALT values on Days 478, 485, 520, 660, 848, 869, and 898 (range: $4.68 \times ULN$ to $9.88 \times ULN$) and AST values on Days 478, 485, 660, 848, 869, and 898 ($2.00 \times ULN$ to $5.48 \times ULN$). Total bilirubin and alkaline phosphatase

values were WNL throughout the trial. The subject was treated with lactulose, sodium chloride, multivitamins (plain), water for injection, calcium carbonate, IV galenic/glucose sodium chloride/potassium chloride, and ergocalciferol. Study drug dose was reduced on Day 890 to a TDD of 10 mg and on Day 898 to a TDD of 5mg due to this event. This event resolved on Day 890 while tapering off study drug. The Investigator considered the AE severe and possibly related to study drug.

Lundbeck provided more information about the above case in their response to Division questions dated 6/17/11. Additional follow up by Lundbeck documented that despite stopping clobazam on study day 912, the patient's transaminases declined but continued to be elevated on day 1024 (ALT 2.68xULN, AST 1.75x ULN). Lundbeck documented that the patient did not have severe hypotension or congestive heart failure that would explain the event. Lundbeck noted that the patient's serology test was weakly positive for CMV, and positive for EBV nuclear antigen antibody. The subject was immunized for Hepatitis A and B. Hepatitis C was non reactive and Hepatitis D and E serologies were not done. Lundbeck also noted that the Celiac profile was negative. Lundbeck stated that a consultant gastroenterologist considered overfeeding and steatohepatitis as a possible etiology. Lundbeck also provided a publication by Mockli et al that described a case of hepatic failure with Phenobarbital (a concomitant medication in this patient) and summarized 13 cases from the literature of hepatitis or hepatic necrosis with Phenobarbital. This patient was also treated with the following concomitant medications that include liver injury information in the package insert: azithromycin, ciprofloxacin, and topiramate.

Lundbeck reported no liver-related AEs in the legacy epilepsy trial.

Lundbeck identified 3 liver-related AEs from the legacy Psychiatry trials (ISS table 7.6.2.4, pp.4726-7). One subject (0001-0004) experienced elevated LFTs and jaundice and was hospitalized and had a liver biopsy that was reportedly consistent with alcoholic cirrhosis (summarized with SAEs above). Subject 001-0171 experienced AEs of liver function test abnormal and aspartate aminotransferase increased. The data listing for this subject documented that the patient's AST at visit 1 was 32U/L and LDH was 174U/L (ALT not reported). At visit 2, AST was 86U/L and LDH was 219U/L. Total bilirubin was normal at both visits. There were no results following visit 2. Subject 001-0099 had an AE of liver disorder. This subject had a visit 1 AST of 12U/L (ULN 44U/L) and ALT of 8 U/L (ULN 24 U/L). At visit 2, AST was 28 U/L and ALT was 25 U/L (ULN 24). At visit 3, AST was 44U/L and ALT was 24U/L. Total bilirubin was not reported.

Lundbeck identified 54 cases of potential liver injury in post marketing reports (see below). There did not appear to be any strong cases suggesting clobazam was the cause of any of the serious hepatic injury events. In the majority of these cases, patients were taking concomitant medications that are recognized as potential hepatotoxins.

Benzodiazepines are not commonly identified as hepatotoxins. In a publication by Ahmed and Siddiqi that reviewed AEDs and liver disease, the authors commented that they "were unable to identify established cases of BDZ-induced hepatotoxicity in the

span of the last 30 years.”¹ I queried PubMed using the search term “clobazam” paired with “hepatotoxicity”, “liver”, “hepatitis”, “hepatic failure”, and “jaundice”. PubMed returned no publications for any of the paired search terms.

Discussion

The evidence presented by Lundbeck does not suggest that clobazam use is associated with liver injury. Although patients experienced elevated transaminases while exposed to clobazam, the risks for transaminase elevations were similar for clobazam and placebo patients in the Phase I or Phase II/III trials. The LGS clinical trials did not include any patients who developed transaminase elevations of at least 3 times upper limit of normal that were associated with elevations of total bilirubin. There did not appear to be any post marketing cases that strongly suggested clobazam resulted in serious hepatic injury. A PubMed search did not identify any case reports or other publications implicating clobazam as the cause of liver injury.

Cancer

Lundbeck found few cancer related AEs in the clobazam safety databases. Lundbeck searched the clobazam safety data using an exhaustive list of AE preferred terms suggesting cancer. Lundbeck found no cancer AEs in the Phase I or Phase II/III controlled trials. In the open label extension trial OV-1004, Lundbeck found the following 3 cancer AEs: benign breast neoplasm, skin papilloma, and osteochondroma (all benign). One subject from the legacy epilepsy trial had a cancer AE. This patient had a low grade astrocytoma and underwent left temporal lobectomy.

Suicidality

The clobazam NDA included limited data to assess suicidality risk. Lundbeck restricted their analysis of suicidality AE data to trials that were randomized, parallel-arm, placebo-controlled; ≥ 20 subjects per treatment arm; duration of ≥ 7 days; subject age ≥ 5 years; and no randomized withdrawal design (criteria established by FDA in the 2005 suicidality analyses). The trials that met these criteria were OV-1012, and the legacy psychiatry trials 205, 215, 220, 225, 400, 405, 410, 415, 425, 435, and 505. There were no suicidality AEs in trial OV-1012. In the legacy psychiatry trials, one clobazam subject discontinued following a suicide attempt and 2 clobazam subjects experienced suicidal ideation.

SUDEP

Lundbeck felt that 3 deaths from trial OV-1004 could potentially be SUDEP. Subject 0017-0107 had chronic lung disease and was found dead in bed. Subject 0018-0607 was found dead in bed. The death event alternative etiology provided by the Investigator was SUDEP. Subject 0008-7059 had a spastic quadriparesis and swallowing disorder and was found at home without pulse or respirations. There were no potential SUDEP cases in the legacy epilepsy trial.

¹ Ahmed SN, Siddiqi ZA. Antiepileptic Drugs and Liver Disease, Seizure. 2006 Apr;15(3):156-64.

DRESS

Lundbeck looked in the clobazam safety databases for cases of drug rash with eosinophilia and systemic symptoms. Lundbeck explained that this syndrome had been referred to by many names (multiorgan hypersensitivity, anticonvulsant hypersensitivity, etc.) and does not have a universally accepted case definition. Lundbeck reported that DRESS does not appear in the labeling for any of the approved benzodiazepines. To look for potential cases of DRESS, Lundbeck searched for AEs related to internal organ involvement (ie, hepatitis, nephritis, pneumonitis, carditis, colitis, encephalitis, pancreatitis, myositis, arthritis, or hematologic system involvement) in association with any one of the following: fever, rash, or lymphadenopathy.

One case from the clinical trials databases met the AE term search criteria and none were identified from the post marketing databases or the medical literature. Subject 0017-7005 who received placebo in the preceding RCT OV-1012, had study drug prematurely discontinued due to an AE of rash. A narrative of the event was presented above, with the discontinuation for AEs. At the time of the event, the subject was receiving clobazam 5mg twice daily. Relevant medical history included upper respiratory infection, fever, and diarrhea. On Day 11 and Day 13, the subject had AEs of rash (mild, severe, respectively). The event description also noted “palpable spleen tip, granulocytopenia (33% seg neutrophils 2% bands with WBC count of $3.4 \times 10^3/\mu\text{L}$), sedimentation rate elevated, anemia (hemoglobin 9.9 g/dL, wnl; HCT 29.5%, LLN 31%), otitis media, liver enzyme elevation (AST 365 U/L normal range 15-60 U/L and ALT 351 U/L normal range 3-35 U/L), and fever” and was diagnosed as “febrile exanthem”. The patient was treated with amoxicillin, paracetamol, ibuprofen, prednisolone, albuterol, and diphenhydramine. The patient’s eosinophil count was 0.1 K/uL (ref range 0.0-0.5 K/uL). Clobazam was stopped on day 17. Central lab results on day 38 and 66 showed that ALT and AST were within normal range (ALT 14 U/L, 17U/L and AST 23U/L, 33U/L, respectively). On Day 66 the rash was described as resolved. Lundbeck reported that a medical review of this case concluded it was not a case of DRESS.

In a 6/3/11 email, the Division asked Lundbeck to discuss why they believe the above described case is not DRESS. In their response, Lundbeck noted that the patient did not experience eosinophilia or lymphadenopathy. Lundbeck felt that in the setting of an upper respiratory tract infection, otitis media, and fever, this event most likely represented an infectious process. Lundbeck thought that the relatively quick resolution argued against DRESS. Lundbeck also noted that DRESS has not been reported for any benzodiazepine AED (6/17/11 Response to Division Questions, pp. 10-11).

Discussion

The clinical trial case that Lundbeck identified using search terms for potential DRESS cases does not appear to be a clear case of DRESS although the lack of consensus in diagnostic criteria complicates evaluation of such cases. While the patient had a rash, fever, and elevated LFTs, he did not have eosinophilia, lymphadenopathy, or other

organ involvement. The event did result in clobazam discontinuation, but the patient was not hospitalized.

I searched PubMed using the term “clobazam” paired with DRESS and drug hypersensitivity syndrome. No publications were identified reporting DRESS/ drug hypersensitivity syndrome implicating clobazam. In a review on the topic of hypersensitivity syndrome and antiepileptic drugs, Hamer and Morris reported that “Hypersensitivity syndrome has not been described in patients taking benzodiazepines...”²

Given the uncertainties about the diagnosis of this case and the lack of other evidence suggesting that clobazam is related to DRESS, I believe, if approved, it would be appropriate to monitor post marketing reports and the literature for DRESS cases with clobazam. I do not believe the evidence warrants placement of DRESS in the labeling of clobazam at this time.

Somnolence Related AEs

During the course of the review, it became clear that somnolence-related AEs were very common in clobazam treated subjects and that the coding of these AEs resulted in splitting of potentially similar events into multiple preferred terms. A review of the AE dataset revealed that the MedDRA 12.0 dictionary included the preferred terms somnolence, hypersomnia, sedation, lethargy and depressed level of consciousness. Since a review of verbatim terms did not indicate an obvious reason for the use of separate preferred terms for these events, the Division asked Lundbeck to reanalyze these AEs. The Division requested analyses that pooled these events into a somnolence-related AE group. The Division also requested additional analyses that summarized time to onset and duration of these events. We also asked Lundbeck to identify predictive factors for these events.

In their 6/17/11 response to the Division’s requests, Lundbeck provided the results of their re-analyses of somnolence-related AEs. In the following table, Lundbeck summarized the frequency of somnolence related events when grouped, and individually. When grouped, the somnolence related events among placebo subjects was 22%, and for clobazam subjects ranged from 28%-44%, with an apparent dose response.

Somnolence-Related AEs from the Controlled Phase II/III LGS Trials

AE	OV-1002		Placebo N=59	OV-1012		
	Clobazam 0.25mg/kg N=32	Clobazam 1.0mg/kg N=32		Clobazam 0.25mg/kg N=58	Clobazam 0.5mg/kg N=62	Clobazam 1.0mg/kg N=59
A least 1	28% (9)	39% (14)	22% (13)	28% (16)	32% (20)	44% (26)

² Hamer HM, Morris HH. Hypersensitivity syndrome to antiepileptic drugs: a review including new anticonvulsants. Cleve Clin J Med. 1999Apr;66(4):239-45.

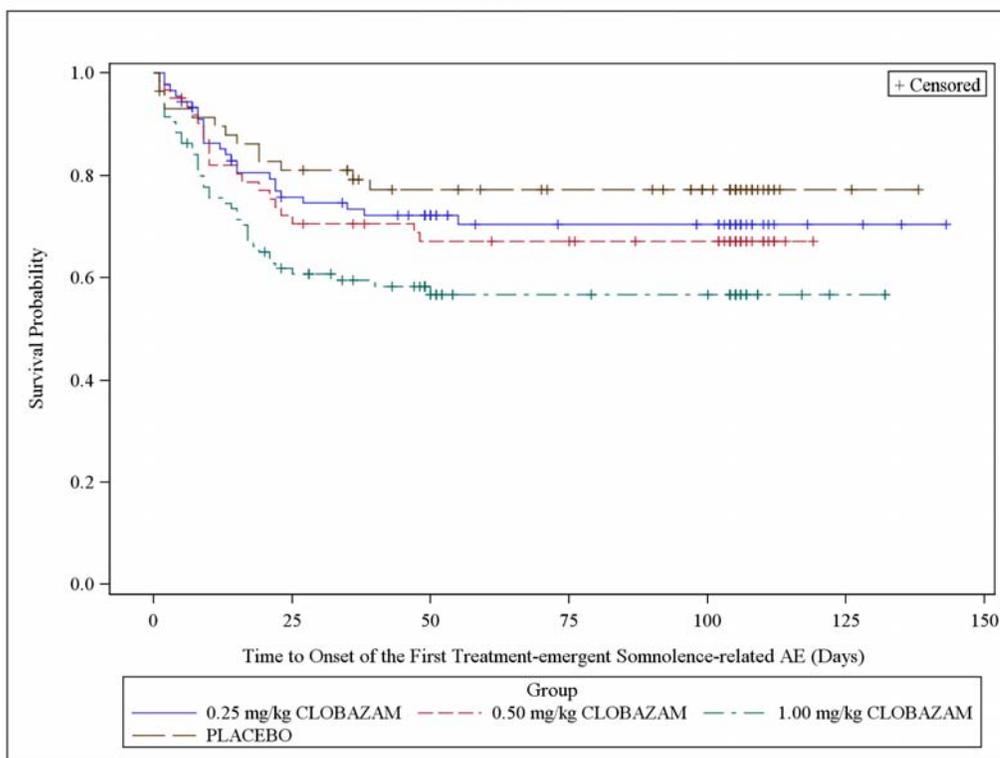
somnolence related AE						
Depressed Level of consciousness	0	2.8% (1)	0	0	0	3.4% (2)
Hypersomnia	0	0	3% (2)	2% (1)	0	0
Lethargy	9% (3)	11% (4)	5% (3)	10% (6)	5% (3)	15% (9)
Sedation	6% (2)	8% (3)	3% (2)	2% (1)	3% (2)	9% (5)
Somnolence	13% (4)	19% (7)	12% (7)	16% (9)	24% (15)	25% (15)

From Table 1, 6/17/11 Submission, p.54

Lundbeck reported that 13 of the 85 clobazam treated subjects with a somnolence related AE discontinued for that event. Lundbeck also noted that the frequency of somnolence-related AEs in the open label trial OV-1004 was 26%, suggesting tolerance to these events over time.

To examine the time to onset for somnolence related events in the LGS controlled trials, Lundbeck created a survival curve. This plot indicates that the majority of the somnolence related events occurred during the first 25 days of treatment, which corresponded to the titration phase of the controlled trials. I provide that figure below.

Figure 1
Time to Onset of the First Treatment-emergent Somnolence-related Adverse Event in Double-blind Phase 2/3 LGS Studies
Safety Population



Lundbeck also provided a survival curve for somnolence related events from the controlled trials and the open label trial. That curve (not shown) demonstrated that relatively few additional somnolence-related AEs were reported after approximately the first 100 days of treatment.

Lundbeck also provided tables 5.1 and 5.2 that demonstrated the trial week when each somnolence related AE was reported and tables 6.1 and 6.2 that demonstrated the prevalence of somnolence related AEs by trial week. Tables 5.1 and 5.2 showed that in both OV-1002 and OV-1012, these events occurred with highest frequency during titration and that few additional events were reported during maintenance (after week 8). Tables 6.1 and 6.2 demonstrated that prevalences for somnolence related events generally peaked around weeks 3-7 and declined by week 12, suggesting tolerance to these effects.

Lundbeck provided information about the duration of the somnolence-related AEs. Using pooled data from the controlled and open label trials, Lundbeck noted that there were a total of 219 reported somnolence-related AEs. Of these, 157 were reported as resolved and 62 as ongoing. In trial OV-1002, somnolence-related events lasted a median of 20 days (range 3-49) in the low dose group compared to a median of 32 days (range 32-76 days) for the high dose group. In trial OV-1012, somnolence related events lasted a median of 26.5 days (range 1-91) in the low dose group, compared to a median of 37.5 days (range 5-104 days) for the middle dose group and a median of 15 days (range 1 to 95 days) for the high dose group. In this same trial, somnolence – related AEs lasted a median of 5.5 days (range 1-92 days) in the placebo group.

To look for predictors of somnolence-related AEs, Lundbeck used logistic regression analyses. Lundbeck reported that for the controlled LGS trials, the odds for somnolence related AEs increased with increasing clobazam dose, Hispanic ethnicity, and for subjects at US investigation sites. For the pooled controlled and open label trial data, Lundbeck found that the odds of experiencing a somnolence-related AE increased with concomitant use of anesthetics and opioids and decreased with concomitant use of rufinamide.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Phase I Trials

Lundbeck reported that 73% (254/349) of the Phase I trial subjects exposed to clobazam experienced one or more treatment emergent AEs (ISS, p.86). In the following table, I identify the adverse events that were reported for 5% or more of clobazam exposed subjects.

Adverse Events Reported by at least 5% of Clobazam Exposed Subjects, Phase I Trials

Treatment Emergent Adverse Event	Clobazam (n=349)
Subjects with 1 or more AE	72.8% (254)
Somnolence	29.2% (102)
Headache	17.5% (61)
Constipation	15.8% (55)
Dizziness	15.5% (54)
Insomnia	8% (28)
Dermatitis contact	6.3% (22)
Tremor	6% (21)
Anxiety	5.7% (20)
Decreased appetite	5.4% (19)

From ISS Table 35, p.89

There were no AEs in Phase I trials coded to the following preferred terms: aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, acute renal failure, acute liver failure, pancreatitis, or rhabdomyolysis.

In all three clobazam phase II/III trials, 92% (277/300) of patients had one or more AEs (120 day Safety Update, p.21). I list the AEs reported by at least 5% of clobazam trial subjects in the following table.

Treatment Emergent AEs Reported by at least 5% of Clobazam Subjects in the Phase II/III Trials

Treatment Emergent AE	Clobazam N=300
Any	92% (277)
Somnolence	25% (76)
Upper respiratory infection	24% (73)
Pyrexia	19% (58)
Pneumonia	15% (44)
Lethargy	14% (43)
Nasopharyngitis	14% (43)
Constipation	14% (41)
Aggression	13% (40)
Fall	13% (39)
Otitis media	13% (39)
Insomnia	12% (35)
Urinary tract infection	11% (34)
Drooling	11% (32)
Sedation	10% (30)
Skin laceration	10% (30)
Convulsion	9% (28)
Viral infection	9% (28)

Diarrhea	9% (27)
Vomiting	8% (25)
Contusion	9% (28)
Irritability	8% (24)
Ataxia	8% (23)
Sinusitis	8% (24)
Decreased appetite	7% (21)
Influenza	7% (20)
Fatigue	6% (19)
Cough	5% (15)
Gastroenteritis	5% (15)
Pharyngitis streptococcal	5% (15)

From 120 day Safety Update Table 6, p.21.

There were no AEs in Phase II/III trials coded to the following preferred terms: aplastic anemia, agranulocytosis, Stevens Johnson Syndrome, Toxic epidermal necrolysis, acute renal failure, acute liver failure, or rhabdomyolysis. Two cases of pancreatitis were discussed above.

In the Phase II/III RCTs, there were small differences in overall AE risk when comparing low dose and high dose clobazam groups in trial OV-1002, and when comparing clobazam and placebo groups in trial OV-1012. In trial OV-1002, 84% (27/32) of low dose patients experienced one or more AEs compared to 86% (31/36) of high dose patients. In trial OV-1012, 68% (40/59) of placebo patients, 72% (42/58) of low dose, 89% (55/62) of medium dose, and 76% (45/59) of high dose clobazam patients experienced 1 or more AEs. Lundbeck noted a dose response for somnolence and constipation with clobazam. In the following table, I summarize the AEs that occurred in at least 5% of clobazam subjects in any dose group.

Treatment Emergent Adverse Events Reported by $\geq 5\%$ of Clobazam Subjects in any dose group in the Phase II/III RCTs

AE	Trial OV-1002		Trial OV-1012			
	Clobazam 0.25mg/kg N=32	Clobazam 1.0 mg/kg N=36	Placebo N=59	Clobazam 0.25mg/kg N=58	Clobazam 0.50mg/kg N=62	Clobazam 1.0 mg/kg N=59
# patients with any AEs	84% (27)	86% (31)	68% (40)	72% (42)	90% (56)	76% (45)
Gastrointestinal disorders	22% (7)	28% (10)	14% (8)	19% (11)	21% (13)	29% (17)
Constipation	3% (1)	8% (3)	0	2% (1)	2% (1)	10% (6)
Diarrhea	3% (1)	3% (1)	7% (4)	7% (4)	3% (2)	5% (3)
Dysphagia	0	0	0	0	0	5% (3)
Salivary hypersecretion	6% (2)	8% (3)	0	2% (1)	0	0
Toothache	6% (3)	0	0	0	0	0
Vomiting	0	6% (2)	5% (3)	9% (5)	5% (3)	7% (4)

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General disorders & administration site conditions	16% (5)	19% (7)	14% (8)	26% (15)	24% (15)	19% (11)
Fatigue	0	0	2% (1)	5% (3)	5% (3)	3% (2)
Irritability	6% (2)	6% (2)	5% (3)	3% (2)	11% (7)	5% (3)
Pyrexia	3% (1)	6% (2)	3% (2)	17% (10)	10% (6)	12% (7)
Infestations & infections	38% (12)	42% (15)	27% (16)	28% (16)	40% (25)	32% (19)
Bronchitis	3% (1)	0	0	2% (1)	0	5% (3)
Gastrointestinal viral infection	6% (2)	0	0	0	0	0
Nasopharyngitis	0	11% (4)	10% (6)	9% (5)	10% (6)	7% (4)
Otitis media	13% (4)	0	0	0	2% (1)	2% (1)
Pneumonia	0	6% (2)	0	3% (2)	3% (2)	2% (1)
Sinusitis	6% (2)	6% (2)	3% (2)	0	0	2% (1)
Upper respiratory tract infection	9% (3)	3% (1)	10% (6)	10% (6)	13% (8)	14% (8)
Urinary tract infection	0	0	0	2% (1)	5% (3)	5% (3)
Viral infection	0	11% (4)	2% (1)	0	0	3% (2)
Viral upper respiratory tract infection	6% (2)	3% (1)	0	2% (1)	2% (1)	0
Injury, poisoning, & Procedural complications	16% (5)	8% (3)	27% (16)	10% (6)	13% (8)	14% (8)
Contusion	6% (2)	0	5% (3)	3% (2)	3% (2)	3% (2)
Skin laceration	6% (3)	6% (2)	5% (3)	2% (1)	0	3% (2)
Metabolism/Nutrition disorders	6% (2)	6% (2)	5% (3)	10% (6)	5% (3)	12% (7)
Decreased appetite	0	3% (1)	3% (2)	3% (2)	0	7% (4)
Increased appetite	0	0	0	2% (1)	3% (2)	5% (3)
Nervous system disorders	38% (5)	50% (15)	29% (17)	33% (19)	48% (30)	58% (34)
Ataxia	6% (2)	3% (1)	3% (2)	3% (2)	2% (1)	10% (6)
Convulsion	9% (3)	3% (1)	0	0	0	0
Drooling	3% (1)	0	3% (2)	0	13% (8)	14% (8)
Dysarthria	0	0	0	2% (1)	2% (1)	5% (3)
Lethargy	9% (3)	11% (4)	5% (3)	10% (6)	5% (3)	15% (9)
Psychomotor hyperactivity	3% (1)	3% (1)	3% (2)	3% (2)	3% (2)	5% (3)
Sedation	6% (2)	8% (3)	3% (2)	2% (1)	3% (2)	9% (5)
Somnolence	13% (4)	19% (7)	12% (7)	16% (9)	24% (15)	25% (15)
Tremor	0	3% (1)	0	2% (1)	7% (4)	2% (1)
Psychiatric disorders	16% (5)	33% (12)	14% (8)	10% (6)	24% (15)	29% (17)
Abnormal behavior	0	6% (2)	2% (1)	2% (1)	2% (1)	2% (1)
Aggression	6% (2)	8% (3)	5% (3)	3% (2)	8% (5)	14% (8)
Hypomania	3% (1)	8% (3)	0	0	0	0

Insomnia	3% (1)	6% (2)	2% (1)	2% (1)	5% (3)	7% (4)
Respiratory, thoracic, & mediastinal disorders	3% (1)	6% (2)	9% (5)	16% (9)	10% (6)	17% (10)
Cough	0	0	0	3% (2)	5% (3)	7% (4)
Nasal congestion	3% (1)	0	2% (1)	5% (3)	0	2% (1)
Skin disorders	6% (2)	0	9% (5)	7% (4)	8% (5)	5% (1)
Rash	0	0	3% (2)	2% (1)	3% (2)	5% (3)

From Table 6/30/11 Table 4.2.2.1.1, pp. 2-24.

In the Legacy epilepsy trial (301), Lundbeck reported that 86% (102/119) of clobazam subjects and 87% (101/116) of active control subjects experienced one or more treatment emergent AEs (ISS, p.99). In the following table, I identify the AEs from trial 301 that occurred in at least 5% of clobazam subjects.

Treatment Emergent AEs Occurring in at least 5% of Clobazam Subjects, Legacy Trial 301

AE	Clobazam (n=119)	Active Control (n=116)
Irritability	45% (53)	38% (44)
Somnolence	39% (46)	39% (45)
Aggression	36% (43)	32% (37)
Attention deficit/hyperactivity disorder	35% (42)	28% (32)
Negativism	34% (40)	27% (31)
Restlessness	29% (35)	22% (26)
Impulsive behavior	25% (30)	14% (16)
Depressed mood	13% (16)	10% (11)
Vomiting	11% (13)	21% (24)
Dizziness	10% (12)	7% (8)
Headache	10% (12)	7% (8)
Ataxia	9% (11)	15% (17)
Drooling	9% (11)	7% (8)
Rash	8% (10)	11% (13)
Social avoidant behavior	8% (10)	11% (13)
Convulsion	7% (8)	4% (5)

From ISS Table 39, p.99.

In addition to above, 1 clobazam subject (0.8%, 1/119) and no active control subjects (0/116) had an AE of pneumonia (ISS Table 4.3, p.3694).

Lundbeck presented the common AE data for the Legacy Psychiatry Trials in 5 separate tables. Lundbeck used their pre-specified groupings of Legacy Psychiatry Trials (described above) to present these data. Below, I summarize the AEs that occurred in at least 5% of clobazam patients in the controlled Legacy Psychiatry trials.

AEs that occurred in at least 5% of clobazam subjects, Controlled Legacy Psychiatry Trials, By Analysis Group

AE	Treatment		
	Placebo (n=68)	Clobazam (n=203)	Diazepam (n=133)
Controlled Legacy Psychiatry Trials, US and Canada			
Any	14.7% (10)	42.9% (87)	54.9% (73)
Somnolence	1.5% (1)	21.2% (43)	32.3% (43)
Dizziness	1.5% (1)	10.8% (22)	6.8% (9)
Headache	1.5% (1)	5.9% (12)	9% (12)
Syncope	0	5.4% (11)	3.8% (5)
Controlled Legacy Psychiatry Trials, Rest of the World			
	Placebo (n=191)	Clobazam (n=395)	Diazepam (n=252)
Any	23.0% (44)	38.0% (150)	36.9% (93)
Somnolence	5.8% (11)	14.9% (59)	18.7% (47)
Fatigue	5.2% (10)	9.4% (37)	16.3% (41)
Dizziness	4.2% (8)	8.9% (35)	13.9% (35)
Dry Mouth	3.7% (7)	6.1% (24)	3.2% (8)
Controlled Legacy Psychiatry Trials, non-CRF			
	Placebo (n=364)	Clobazam (n=615)	Diazepam (n=453)
Any	34.9% (127)	40.7% (250)	46.1% (209)
Somnolence	12.9% (47)	19.2% (118)	26.5% (120)

From ISS tables 4.4.1, 4.4.2, 4.4.3, pp. 3704-3731.

In the following table, I summarize the AEs occurring in at least 10% of clobazam patients in the uncontrolled Legacy Psychiatry Trials.

AEs that occurred in at least 10% of clobazam subjects, Uncontrolled Legacy Psychiatry Trials, By Analysis Group

Uncontrolled Legacy Psychiatry Trials, CRF	
	Clobazam (n=200)
Any	23.5% (47)
Somnolence	11.0% (22)
Uncontrolled Legacy Psychiatry Trials, non-CRF	
	Clobazam (n=71)
Any	63.4% (45)
Irritability	42.3% (30)
Tension headache	39.4% (28)
Asthenia	18.3% (13)
Fatigue	18.3% (13)
Memory impairment	16.9% (12)
Tension	16.9% (12)

Initial insomnia	15.5% (11)
Dyspepsia	14.1% (10)
Middle insomnia	14.1% (10)
Myalgia	12.7% (9)

From ISS tables 4.4.4 and 4.4.5, pp. 3732-3741.

Pneumonia was not reported as an AE for any patients in the legacy Psychiatry trials.

7.4.2 Laboratory Findings

In their NDA presentation, Lundbeck separately summarized hematology, chemistry, and urinalysis results.

For the Phase I trials, Lundbeck identified patients with potentially clinically significant (PCS) lab results that were associated with AEs. Lundbeck did not provide shift tables or mean change from baseline analyses for Phase I trials.

For the Phase II/III trials (OV-1002, OV-1012), Lundbeck identified PCS lab results, and provided lab result shift tables, and mean change from baseline analyses. In trial OV-1002, investigators collected hematology and chemistry samples at baseline, week 3 (end of titration), week 7, and week 11 (end of taper). In trial OV-1012, investigators collected hematology and chemistry samples at baseline, week 3 (end of titration), week 7, week 11, and week 15 (end of taper). Lundbeck also provided pooled laboratory results for the controlled and open label Phase II/III trials. I do not focus on these results given the lack of comparative value of such data and difficulty in interpreting data pooled from controlled and open label trials.

For the Legacy Epilepsy Trial 301, Lundbeck identified PCS lab result outliers, and provided lab result shift tables, and mean change from baseline analyses. The study report for Legacy Trial 301 explained that laboratory data were required by protocol only for the screening visit (Study report 301, p.30). Investigators collected post screening labs only in cases that they deemed necessary. As a result, the lab data analyses are based on selected populations and do not represent comparisons of randomized groups.

For the Legacy Psychiatry trials, Lundbeck identified PCS lab result outliers, and provided lab result shift tables, and mean change from baseline analyses. There are limited laboratory data available from the Legacy Psychiatry Trials. In the Controlled Legacy Psychiatry Trials, US and Canada about half of the 203 clobazam subjects had available lab data for analysis. In the Controlled Legacy Psychiatry Trials, Rest of the World, less than 10% of the 395 clobazam patients had lab data. In the Controlled non-CRF trials, roughly 10% of the 615 clobazam patients had hematology lab data. The missing lab data are due to several factors. Some trials simply did not collect laboratory data. In trials that collected laboratory data, investigators did not uniformly collect/report

follow up data. In addition, all of the trials in a particular analysis group did not perform the same tests on each subject, meaning that for a given parameter, only a subset of subjects within an analysis group might have been tested. (ISS p.45).

Hematology

Phase I trials

I reviewed ISS table 8.1.2, which identified all subjects from Phase I trials with PCS hematology results. Eighteen clobazam subjects (5.2%, 18/349) had a PCS low hematocrit result. The lowest hematocrit result among these subjects was 31%. For 11 of the 18 subjects, hematocrit improved and was not PCS at the end of the trial. For the remaining 7 patients, the PCS value was present at the last visit. In these same trials, only 1 subject had a PCS low hemoglobin result. This subject had a baseline hemoglobin of 12.4g/dL, and had a result that met the low PCS criteria (result 11.5g/dL, criteria ≤ 11.5 g/dL) at the last visit. No clobazam subjects from Phase I trials had a platelet result that met the low PCS criteria.

Phase II/III Controlled Trials

There appeared to be an excess of low hemoglobin/hematocrit PCS outliers among clobazam patients compared to placebo in Trial OV-1012, although the small sample sizes and number of events preclude firm conclusions. The PCS data did not support an increased risk of low platelets in clobazam patients in these trials. I provide ISS table 65 that summarizes PCS hematology results for the Phase II/III controlled trials.

Table 65. Incidence of Potentially Clinically Significant Hematology Values in Double-blind Phase 2/3 LGS Studies

Parameter (unit)	Number (%) of Subjects											
	Study OV-1002				Study OV-1012							
	Clobazam Dose Level				Placebo (N = 59)		Clobazam Dose Level					
	Low (N = 32)		High (N = 36)				Low (N = 58)		Medium (N = 62)		High (N = 59)	
Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	
RBC count ($\times 10^{12}/L$)	0	0	0	0	0	0	0	0	1 (1.6)	0	2 (3.4)	0
Hemoglobin (g/dL)	1 (3.1)	0	6 (16.7)	0	3 (5.1)	0	1 (1.7)	0	5 (8.1)	0	10 (16.9)	0
Hematocrit (%)	7 (21.9)	0	8 (22.2)	0	7 (11.9)	0	8 (13.8)	0	16 (25.8)	0	16 (27.1)	0
WBC count ($\times 10^9/L$)	0	0	0	0	0	2 (3.4)	1 (1.7)	1 (1.7)	1 (1.6)	2 (3.2)	1 (1.7)	4 (6.8)
Neutrophils (%)	1 (3.1)	N/A	1 (2.8)	N/A	0	N/A	0	N/A	0	N/A	1 (1.7)	N/A
Lymphocytes (%)	0	1 (3.1)	0	1 (2.8)	1 (1.7)	0	1 (1.7)	0	0	0	0	1 (1.7)
Monocytes (%)	N/A	0	N/A	1 (2.8)	N/A	0	N/A	0	N/A	2 (3.2)	N/A	1 (1.7)
Eosinophils (%)	N/A	0	N/A	0	N/A	3 (5.1)	N/A	5 (8.6)	N/A	2 (3.2)	N/A	3 (5.1)
Platelets ($\times 10^9/L$)	0	1 (3.1)	1 (2.8)	1 (2.8)	0	0	0	1 (1.7)	1 (1.6)	0	0	1 (1.7)

N/A = not applicable; RBC = red blood cell; WBC = white blood cell.

Note: Low-, Medium-, and High-dose levels correspond to target doses of 0.25 mg/kg of clobazam (up to a maximum daily dose of 10 mg), 0.5 mg/kg of clobazam (up to a maximum daily dose of 20 mg), and 1.0 mg/kg (up to a maximum daily dose of 40 mg), respectively.

I examined ISS table 8.2.2.7 which provided lab data for subjects with hematologic PCS results. For the subjects with PCS low hematocrit and hemoglobin values, the declines were small, and in most cases returned to normal either during the controlled trial or the subsequent open label trial. The lowest on-treatment hemoglobin in a clobazam treated patient in the controlled trials occurred in subject OV-1002-0003-0104. This subject had a baseline hemoglobin of 8.4g/dL that dropped to 7.9 g/dL and returned to 8.2g/dL at the last visit.

ISS Table 64 was a shift table for hematological lab test results. In this table, the percentages of patients that shifted from high or normal at baseline to low for hematocrit and hemoglobin were similar when comparing placebo and clobazam patients in trial OV-1012. I provide information from table 64 below.

Shifts from normal or high at baseline to low for select hematologic lab tests in the Phase II/III Controlled trials

Parameter	OV-1002		OV-1012		
	Clobazam dose		Placebo N=59	Clobazam dose	
	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62

RBC shift to low	0	19.4% (7)	16.9% (10)	8.6% (5)	16.1% (10)	16.9% (10)
Hemoglobin shift to low	6.3% (2)	19.4% (7)	15.3% (9)	12.1% (7)	12.9% (8)	18.6% (11)
Hematocrit shift to low	12.5% (4)	8.3% (3)	15.3% (9)	15.5% (9)	22.6% (14)	22% (13)
WBC shift to low	9.4% (3)	16.7% (6)	6.8% (4)	12.1% (7)	11.3% (7)	6.8% (4)
Platelet shift to low	0	16.7% (6)	10.2% (6)	5.2% (3)	11.3% (7)	13.6% (8)

Lundbeck summarized mean changes from baseline to final visit for the hematologic tests in the controlled Phase II/III trials. I provide those results in the following table. The mean changes tended to be small and of unknown clinical significance.

Parameter	OV-1002		OV-1012			
	Clobazam dose		Placebo N=59	Clobazam dose		
	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62	1.0mg/kg N=59
RBC (x10 ¹² /L)	-0.07	-0.26	-0.01	0.07	-0.13	-0.14
Hemoglobin g/dL	-0.26	-0.75	0.09	0.24	-0.30	-0.39
Hematocrit %	-1.1	-1.9	-0.1	0.3	-1.3	-1.1
WBC (x10 ⁹ /L)	-0.27	-0.12	0.0	-0.18	-0.82	-0.07
Platelet (x10 ⁹ /L)	-15.5	0.2	-0.9	-13.2	-16.2	-15.3

From ISS table 8.2.2.1

Legacy Epilepsy Trial 301

As noted above, the study report for Legacy Trial 301 explained that laboratory data were required by protocol only for the screening visit. The following hematologic lab data analyses are based on selected populations and do not represent comparisons of randomized groups.

In the Legacy Epilepsy Trial 301, 3 (9.1%, 3/33) clobazam and 3 (7.9%, 3/38) active comparator subjects experienced PCS low hematocrit values. No tested subjects in this trial had a PCS low hemoglobin result. In addition, no tested subjects in trial 301 experienced low PCS results for WBCs or platelets.

Based on the available data, when comparing clobazam and active treatment groups, there did not appear to be differences in risk for shifts from normal or high at baseline to low for hematocrit (clobazam 6.1%, 2/33; active 5.3%, 2/38), or hemoglobin (clobazam 5.9%, 2/34; active 5.3%, 2/38). One clobazam subject (2.9%, 1/34) and 2 active treatment subjects (5.3%, 2/38) experienced WBC shifts from high/normal at baseline to low during the trial. No clobazam and no active treatment patients experienced low platelet shifts during the trial (ISS table 8.2.2.13.2).

Lundbeck provided the mean changes from baseline for hematologic tests. There did not appear to be meaningful differences in mean changes when comparing clobazam and active treatment groups. I provide the mean changes in the following table.

Mean change from baseline to final; select hematologic labs, Legacy Trial 301

Parameter	Clobazam	Active Control
Hematocrit (%)	1.5 (n=33)	0.4 (n=38)
Hemoglobin (g/dL)	0.33 (n=34)	0.12 (n=38)
Leukocytes (x10 ⁹ /L)	1.17 (n=34)	-0.43 (n=38)
Platelets (x10 ⁹ /L)	-14.6 (n=34)	-19.6 (n=38)

From ISS table 8.2.2.13.1

Legacy Psychiatry trials

Lundbeck summarized lab test results from the Legacy Psychiatry trials using the same data groupings used in other sections of the ISS. Laboratory data are available for only a subset of subjects from these trials, limiting any conclusions about the effect of clobazam on hematologic lab parameters. In the Controlled Legacy Psychiatry Trials, US and Canada, about half of the subjects in any treatment group had available lab data for analysis. In the Controlled Legacy Psychiatry Trials, Rest of the World, 29 of 395 clobazam patients had lab data. In the Controlled non-CRF trials, roughly 10% (61/615) of the clobazam patients had lab data.

Lundbeck identified few patients with PCS hematology lab results from the Legacy Psychiatry Trials. In the following table, I identify select PCS hematology results. Hemoglobin and hematocrit were not reported for the Controlled Legacy Psychiatry Trials, Rest of the World.

Select PCS Hematology Results from Legacy Psychiatry Trials

AE	Treatment		
Controlled Legacy Psychiatry Trials, US and Canada			
Parameter	Placebo (n=68)	Clobazam (n=203)	Diazepam (n=133)
Hematocrit low	0	2.3% (3/118)	5.6% (4/71)
Hemoglobin low	0	1.6% (2/128)	0
Leukocytes low	0	0	2.3% (1/44)
Controlled Legacy Psychiatry Trials, Rest of the World			

	Placebo (n=191)	Clobazam (n=395)	Diazepam (n=252)
Leukocytes low	0	0	3.4% (1/29)
Platelets low	0	0	0
Controlled Legacy Psychiatry Trials, non-CRF			
	Placebo (n=364)	Clobazam (n=615)	Diazepam (n=453)
Hematocrit low	0	1.6% (1/61)	1.9% (1/52)
Hemoglobin low	0	0	0
Leukocytes low	0	0	0

From ISS Tables 8.2.2.14.3, 8.2.2.15.3, and 8.2.2.16.3.

Lundbeck provided shift table hematology results for the legacy Psychiatry trials. As above, the incomplete lab data limit any conclusions about the effect of clobazam on hematological lab parameters. For this analysis, Lundbeck reported no data for the Controlled Legacy Psychiatry Trials, Rest of the World.

Shift from high/normal to low, Hematology Tests from Legacy Psychiatry Trials

AE	Treatment		
Controlled Legacy Psychiatry Trials, US and Canada			
Parameter	Placebo (n=68)	Clobazam (n=203)	Diazepam (n=133)
Hematocrit %	13.5% (7/52)	14.8% (19/128)	22.5% (16/71)
Hemoglobin (g/dL)	3.8% (2/52)	6.3% (8/128)	7% (5/71)
Leukocytes (x10 ⁹ /L)	3.8% (2/52)	2.9% (3/102)	9.1% (4/44)
Controlled Legacy Psychiatry Trials, non-CRF			
	Placebo (n=364)	Clobazam (n=615)	Diazepam (n=453)
Hematocrit %	8% (2/25)	6.6% (4/61)	11.5% (6/52)
Hemoglobin (g/dL)	0	4.9% (3/61)	7.7% (4/52)
Leukocytes (x10 ⁹ /L)	0	3.3% (2/61)	3.8% (2/52)

From Tables 8.2.2.14.2, 8.2.2.15.2, and 8.2.2.16.2

The following table summarizes mean change from baseline to final for select hematology lab tests from the Legacy Psychiatry Trials.

Mean change from baseline to final, Hematology Tests from Legacy Psychiatry Trials

AE	Treatment		
Controlled Legacy Psychiatry Trials, US and Canada			
Parameter	Placebo (n=68)	Clobazam (n=203)	Diazepam (n=133)
Hematocrit %	-0.9 (n=52)	-0.6 (n=128)	-1.0 (n=71)
Hemoglobin (g/dL)	-0.14 (n=52)	-0.48 (n=128)	0.02 (n=71)
Leukocytes (x10 ⁹ /L)	-1.63 (n=52)	-0.05 (n=102)	-0.17 (n=44)
Controlled Legacy Psychiatry Trials, Rest of the World			
	Placebo (n=191)	Clobazam (n=395)	Diazepam (n=252)
Leukocytes (x10 ⁹ /L)	0.14 (n=27)	-0.20 (n=29)	-0.73 (n=29)
Platelets (x10 ⁹ /L)	1.6 (n=25)	0.9 (n=25)	8.0 (n=28)

Controlled Legacy Psychiatry Trials, non-CRF			
	Placebo (n=364)	Clobazam (n=615)	Diazepam (n=453)
Hematocrit %	0.0 (n=25)	-0.7 (n=61)	-0.7 (n=52)
Hemoglobin (g/dL)	0.05 (n=25)	-0.27 (n=61)	-0.26 (n=52)
Leukocytes (x10 ⁹ /L)	.40 (n=25)	-0.57 (n=61)	-0.24 (n=52)

From ISS Tables 8.2.2.14.1, 8.2.2.15.1, 8.2.2.16.1

Chemistry

I reviewed ISS table 8.1.1.1, which listed all Phase I trial subjects with PCS chemistry results. Twelve clobazam subjects and one placebo subject experienced PCS chemistry results. For the 12 clobazam subjects, 3 experienced PCS ALT and AST and 1 experienced PCS ALT. Two clobazam subjects experienced PCS creatinine results and 2 experienced PCS triglyceride results. One clobazam subject experienced PCS results for each of the following analytes: Calcium, BUN, Potassium, and urate. The placebo subject experienced PCS ALT results.

Phase II/III Controlled Trials

PCS chemistry results were infrequent in the Phase II/III controlled trials and in trial OV-1012, there did not appear to be strong evidence of differences in risk when comparing clobazam and placebo. In the following table I provide PCS results for select chemistry parameters in the Phase II/III controlled trials.

PCS results for select chemistry parameters in the Phase II/III controlled trials

Parameter	OV-1002		OV-1012			
	Clobazam dose		Placebo N=59	Clobazam dose		
	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62	1.0mg/kg N=59
ALT High	3.1% (1)	2.8% (1)	1.7% (1)	0	0	0
AST High	3.1% (1)	2.8% (1)	1.7% (1)	0	0	0
ALP High	0	0	1.7% (1)	1.7% (1)	3.2% (2)	6.8% (4)
Bilirubin high	0	0	0	0	0	0
Bicarbonate Low	0	0	5.1% (3)	1.7% (1)	4.8% (3)	1.7% (1)
BUN High	0	2.8% (1)	0	0	1.6% (1)	1.7% (1)
Calcium Low	0	0	1.7% (1)	1.7% (1)	0	1.7% (1)
Sodium High	0	0	0	0	0	3.4% (2)

From ISS Table 8.2.1.3.1

For each of the remaining parameters not listed, there was either 1 or no clobazam subjects with a PCS result.

ISS Table 70 was a shift table for chemistry lab test results. In trial OV-1012, the risk for shifting from normal or low at baseline to high was similar for clobazam and placebo for ALT and ALP. For AST, a higher percentage of clobazam patients shifted higher. The data also demonstrate somewhat higher risks among clobazam subjects for shifts higher for calcium, sodium and triglycerides. In the following table, I provide shift results for select chemistry parameters.

Shift results for select chemistry parameters in the Phase II/III controlled trials

	OV-1002		OV-1012			
	Clobazam dose		Placebo N=59	Clobazam dose		
Parameter	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62	1.0mg/kg N=59
ALT High	6.3% (2)	13.9% (5)	10.2% (6)	5.2% (3)	4.8% (3)	6.8% (4)
AST High	12.5% (4)	8.3% (3)	3.4% (2)	8.6% (5)	6.5% (4)	16.9% (10)
ALP High	9.4% (3)	22.2% (8)	8.5% (5)	8.6% (5)	11.3% (7)	6.8% (4)
Bilirubin high	0	0	1.7% (1)	0	0	0
Bicarbonate Low	6.3% (2)	2.8% (1)	32.2% (19)	13.8% (8)	11.3% (7)	15.3% (9)
BUN High	0	2.8% (1)	1.7% (1)	0	4.8% (3)	10.2% (6)
Calcium High	6.3% (2)	8.3% (3)	8.5% (5)	12.1% (7)	9.7% (6)	13.6% (8)
Sodium High	3.1% (1)	5.6% (2)	3.4% (2)	5.2% (3)	3.2% (2)	10.2% (6)
Triglycerides High	12.5% (4)	30.6% (11)	5.1% (3)	12.1% (7)	16.1% (10)	8.5% (5)

From ISS Table 8.2.1.2

In trial OV1012, the mean changes from baseline to final were generally similar for clobazam and placebo subjects. Two exceptions were ALP and triglycerides, where the mean change was positive among clobazam patients and negative among placebo patients. I provided select chemistry mean change results in the following table.

Mean change from baseline to final for select chemistry parameters in the Phase II/III controlled trials

	OV-1002		OV-1012			
	Clobazam dose		Placebo N=59	Clobazam dose		
Parameter	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62	1.0mg/kg N=59
ALT U/L	9.4	2.8	0.4	0.9	0.4	-0.2
AST U/L	7.2	1.7	1.1	0.5	0.9	1.3

ALP U/L	-1.9	8.3	-5.3	9.9	13.2	11.3
Bilirubin mg/dL	0.0	0.0	0.0	0.0	0.0	0.0
Bicarbonate mEq/L	-0.8	0.0	-1.1	0.2	-0.4	0.3
BUN mg/dL	0.3	0.3	0.4	0.6	0.2	0.6
Calcium mg/dL	-0.1	-0.1	0.0	0.1	0.0	-0.1
Sodium mEq/L	0.0	0.8	0.2	0.0	0.4	-0.1
Triglycerides mg/dL	3.3	24.2	-6.9	8.5	18.1	9.4

From Table 8.2.1.1

Legacy Epilepsy Trial 301

As explained above for hematology, chemistry tests were required by protocol only for the screening visit, therefore limited lab data are available for subjects who participated in the Legacy Epilepsy trial. Lundbeck reported that only 1 clobazam subject had a PCS chemistry result (ALP high). Shift results and mean changes from baseline were generally similar for clobazam and placebo subjects although these results should be interpreted cautiously given that they are based on a selected subset of the trial population (ISS tables 8.2.1.13.1, 8.2.1.13.2, 8.2.1.13.3, and 8.2.1.13.4).

Legacy Psychiatry Trials

As noted above, lab data results are available for only a subset of the study subjects in the Legacy Psychiatry Trials analysis groups. Lundbeck reported that PCS chemistry results were rare in the Legacy Psychiatry trials. In the North American controlled trials, the only chemistry parameters that had more than 1 clobazam subject with a PCS result were low glucose (2/88) and high BUN (2/100) (ISS table 8.2.1.14.3). In the Controlled non CRF trials, the only chemistry parameters that had more than 1 clobazam subject with a PCS result were low albumin (2/63) and low phosphate (2/61) (8.2.1.16.3). No subjects from the remaining legacy psychiatry trials had a PCS chemistry result (ISS, p.162). Shift results and mean changes from baseline were generally similar for clobazam, placebo, and active comparator subjects, although these results should be interpreted cautiously given that they are based on a selected subset of subjects within the analysis groups.

Urinalysis

In the Phase I trials, for clobazam exposed subjects, the mean changes (pH and specific gravity) and shifts to abnormal for the urine parameters were small and likely of little clinical significance (ISS tables 8.3.2.1.1, 8.3.2.1.2, 8.3.2.2.1, 8.3.2.2.2).

In the Phase II/III controlled trials, shifts from normal at baseline to abnormal for urine parameters were infrequent (ISS table 8.3.2.3.2, 8.3.2.4.1, 8.3.2.4.2). There did not

appear to be meaningful differences in shift from normal to abnormal when comparing clobazam and placebo subjects in trial OV-1012. The mean changes from baseline to final for pH and specific gravity were similar for clobazam and placebo subjects in trial OV-1012 (ISS table 8.3.2.3.1).

Urinalysis data from the legacy trials included listings of results and provided little useful information.

7.4.3 Vital Signs

For Phase I trials, Lundbeck identified the clobazam exposed subjects who had one or more PCS vital sign results. For Phase II/III controlled trials, Lundbeck provided mean change from baseline, and PCS result analyses. Lundbeck provided similar analyses for vital sign data from the pooled controlled and open label Phase II/III trials. I do not focus on these analyses given the difficulty in interpreting pooled controlled trial and open label data. Investigators did not record vital signs during the Legacy trials.

Phase I trials

Lundbeck reported that 7 subjects (5 clobazam, 2 placebo) had one or more PCS vital sign results during Phase I trials (5 from trial OV-1022, 1 from trial OV-1017, and one from trial OV-1018).

During OV-1022, the formal QT trial, which administered clobazam doses of 40mg and 160mg/day, 2 clobazam and 2 placebo subjects experienced high pulse rates (highest 168bpm). All four subjects were reported to have sinus tachycardia AEs. None of these subjects experienced AEs of dizziness, hypotension, syncope, or loss of consciousness. The 2 clobazam subjects were in the 40mg dose group and neither was a CYP2C19 poor metabolizer. In trial OV-1018, one clobazam subject had PCS pulse rates (highest 145bpm) and an AE of sinus tachycardia on study Day 14. The event resolved the same day and the subject did not experience dizziness, hypotension, syncope, or loss of consciousness (ISS p.164 and AE dataset).

Also during OV-1022, 1 subject experienced low systolic and diastolic BP results. Subject 001-1008, receiving 160mg/day, had a baseline BP of 109/67mmHg, and during the trial had systolic BPs of 67, 77, and 89 mmHg and a diastolic BP of 46mmHg. This subject had recorded AEs of hypotension and dizziness on the same day. These events resolved on the next day.

In OV-1017, 1 subject experienced a PCS high diastolic BP of 105mmHg. This subject had an AE of blood pressure increased and the event was resolved on day 21.

Phase II/III Controlled Trials

Lundbeck's mean change from baseline to final analysis did not appear to demonstrate consistent clobazam related vital sign changes. I summarize results from that analysis in the table below.

Mean change from baseline to final for vital sign parameters in the Phase II/III controlled trials

	OV-1002		OV-1012			
	Clobazam dose		Placebo N=59	Clobazam dose		
Parameter	0.25mg/kg N=32	1.0mg/kg N=36		0.25mg/kg N=58	0.5mg/kg N=62	1.0mg/kg N=59
Systolic BP mmHg	0.0	-1.1	-0.6	1.7	1.2	1.9
Diastolic BP mmHg	1.4	-3.0	0.3	-4.2	-0.4	0.4
Pulse bpm	-6.2	0.6	-1.1	-2.9	-4.2	1.2

From ISS Table 74

Lundbeck's PCS analysis did not appear to demonstrate consistent clobazam related vital sign changes. I summarize results from that analysis in the table below.

PCS for vital sign parameters in the Phase II/III controlled trials

	OV-1002				OV-1012								
	Clobazam dose				Placebo N=59	Clobazam dose							
	0.25mg/kg N=32		1.0mg/kg N=36			0.25mg/kg N=58		0.5mg/kg N=62		1.0mg/kg N=59			
Parameter	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High	
Systolic BP mmHg	9% (3)	0	11% (4)	0	9% (5)	0	10% (6)	0	16% (10)	0	15% (9)	0	
Diastolic BP mmHg	16% (5)	0	25% (9)	0	10% (6)	0	16% (9)	0	8% (5)	2% (1)	12% (7)	0	
Pulse bpm	0	13% (4)	0	28% (10)	0	14% (8)	0	16% (9)	0	8% (5)	3% (2)	19% (11)	

From ISS Table 75

7.4.4 Electrocardiograms (ECGs)

Lundbeck's ECG data for clobazam come from the formal QT trial, OV-1022, and from ECGs that were performed during controlled trial OV-1012. Lundbeck did not find evidence of QT prolongation with clobazam or its metabolite, N-desmethylclobazam in OV-1022. The ECGs from OV-1012 did not suggest repolarization prolongation in patients treated with clobazam.

Trial OV-1022

Lundbeck's NDA submission included results from a formal QT study that examined the effect of clobazam on cardiac repolarization. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed OV-1022 in a 8/9/11 memo. The IRT reported the following:

- No significant QTc prolongation effect of clobazam (40 mg and 160 mg) was detected in this TQT study.
- The largest upper bounds of the 2-sided 90% CI for the mean difference post-dose between clobazam (40 mg and 160 mg) and placebo were below 10 ms, the threshold for regulatory concern
- After administration of moxifloxacin, the largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was 7.1 ms.
- The suprathreshold dose (160 mg) produces mean clobazam C_{max} values 2.7-fold and N-desmethyloclobazam C_{max} values 3.9-fold the mean C_{max} for the 40-mg dose, the therapeutic dose. The highest clinical exposure scenario is administration of clobazam with alcohol which increases C_{max} 50%. The largest drug interactions have been with ketoconazole (50% increase in AUC) and omeprazole (40% increase in AUC, 15% increase in C_{max}). The exposures observed in this study following the 160-mg dose cover these scenarios.

The IRT recommended the following labeling to summarize the results of the formal QT study:

12.2 Pharmacodynamics

The effect of clobazam 20 mg and 80 mg administered twice daily on QTc interval was evaluated in a randomized, evaluator blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 80 mg twice daily is adequate to represent the high exposure clinical scenario.

Trial OV-1022 was a double-blind, randomized, single-site, 4-arm, parallel-group trial that evaluated the effects of clobazam and moxifloxacin (positive control) relative to placebo on the QT interval in 280 healthy volunteers at the potential therapeutic dose (clobazam 40 mg TDD) and at 4 times the proposed therapeutic dose (clobazam 160 mg TDD). The primary endpoint of trial OV-1022 was the time-matched, placebo-corrected mean change from baseline in Fridericia corrected QT interval (QTcF) during the 24-hour collection period on Day 29.

Lundbeck reported that moxifloxacin met the criteria for assay sensitivity for QTc prolongation (time-matched, placebo-corrected changes from baseline mean estimates

for QTcF were greater than 5 ms at all of the time points between 1 and 16 hours postdose, inclusive, and lower bound of the 2-sided Bonferroni-adjusted 90% confidence interval for the largest time-matched mean estimate was 11.6 ms at 4 hours).

Lundbeck reported that the time-matched mean estimates for the differences in QTcF between clobazam and placebo (baseline-adjusted) were negative. In addition, all of the upper bounds of the 2-sided 90% confidence intervals for these QTcF estimates were below 5 ms, (highest postdose upper bounds of 0.1 ms for clobazam 40 mg TDD at 3 hours post dose and -1.0 ms at 6 hours postdose for clobazam 160 mg TDD).

For outliers, Lundbeck reported that no subjects who received clobazam had QTc intervals above 480 ms, or experienced changes from baseline in QTc intervals that were greater than 60 ms. In addition, none of the subjects receiving clobazam had clinically important changes noted in his/her ECG morphology.

Lundbeck found no PK/pharmacodynamic relationship between clobazam or N-desmethyclobazam (N-CLB) plasma concentrations and QTc prolongation.

OV-1012

Investigators collected ECGs at screening, baseline (a total of 4 time points), week 5 (3 time points), week 7 (one time point) and week 15 (one time point). Lundbeck had eReaseach Technology read the ECGs using digital techniques. eReaseach Technology found no abnormality in heart rate, atrio-ventricular conduction, or cardiac depolarization. In addition, the eReaseach Technology reported no signal of prolongation of QTcF and no new morphological changes were noted that represented a clear signal of an effect from clobazam.

In the following table, I summarize the QTcF outliers from the analysis of ECG data from OV-1012.

QTcF Outliers by Treatment from OV-1012

	Placebo (N=58)	Clobazam		
Outlier criteria		0.25mg/day (n=56)	0.5mg/day (n=62)	1.0mg/day (n=55)
QTcF>480ms	0	0	0	0
QTcF increase 30-60ms	3.4% (2)	5.4% (3)	8.1% (5)	9.1% (5)
QTc increase>60msec	0	0	0	0

From the Cardiac Safety Report for OV1012, p.12

In the following table, I summarize the mean change from baseline results for the ECG data from OV-1012

Mean Change from Baseline Results for the ECG Data from OV-1012

Mean change from baseline*	Placebo	Clobazam		
	(N=58)	0.25mg/day (n=56)	0.5mg/day (n=62)	1.0mg/day (n=55)
Heart rate	-0.2	0.2	-0.1	1.2
QT	3.1	-2.7	1.0	-0.5
QTcB	1.6	-3.0	1.5	1.8
QTcF	2.1	-2.9	1.3	0.9

From the Cardiac Safety Report for OV1012, p.12

*Average of all ECGs collected during screening/baseline was compared to the average of all on treatment ECG values.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

To explore dose-response relationship for AEs, Lundbeck summarized AE data from 2 Phase I trials, Phase II/II controlled trials, and concentration-response analyses using population pharmacokinetics data.

Phase I trials

Lundbeck analyzed data from Phase I trial OV-1038, where 24 healthy adults given clobazam were titrated up to 80mg bid over a 44 day period. In this trial, 3 subjects discontinued for AEs. One subject withdrew for dizziness and somnolence while receiving 70mg BID. One subject withdrew for somnolence while receiving 60mg BID. The third subject withdrew for elevated transaminases while receiving 10 and 15mg BID. None of these 3 subjects were CYP2C19 poor metabolizers. When looking at overall AE risks by dose, there did not seem to be a clear dose response. AEs risks ranged from 4% (40mg BID and 50mg BID doses) to 42% (10mg BID dose). At the three highest clobazam doses, the AE risks were 22% (60mg BID dose), 17% (70mg BID dose), and 18% (80mg BID dose). Contact dermatitis, constipation, dizziness, and somnolence were the only AEs reported by at least 3 subjects in this trial. For the 4 subjects with somnolence AEs, the events were reported at the following clobazam doses: 20mg BID, 25mg BID, 60mg BID, and 70mg BID.

Trial OV-1022, the formal QT trial, had 4 treatment groups, each with 70 subjects. In addition to the placebo and moxifloxacin treatment groups, there were 2 clobazam treatment groups, one administered 20mg BID and one administered 80mg BID. Investigators titrated the clobazam subjects to their final dose over a 28 day period. Ten clobazam subjects discontinued for AEs (3 in the 20mg BID group, 7 in the 80mg BID

group) compared to 2 placebo and 1 moxifloxacin subjects. In the clobazam 20mg BID group, 2 subjects discontinued for transaminase elevations and one for mental status changes. In the clobazam 80mg BID group, 2 subjects discontinued for delirium, and one subject each for the following AEs: somnolence; delirium and depressed mood; decreased libido, erectile dysfunction, and insomnia; dysarthria and unsteady gait; dizziness. In the following table, I identify the AEs that occurred in at least 5% of clobazam subjects and that were twice as common in the 80mg BID group compared to the 20mg BID group.

AEs that Occurred in at Least 5% of Clobazam Subjects and that were at least twice as common in the 80mg BID group compared to the 20mg BID group, Trial OV-1022

AE	Clobazam 20mg BID N=70	Clobazam 80mg BID N=70	Placebo N=70	Moxifloxacin N=70
Any	81% (57)	93% (65)	67% (47)	66% (46)
Somnolence	13% (9)	33% (23)	3% (2)	6% (4)
Dizziness	7% (5)	31% (22)	7% (5)	6% (4)
Dysarthria	1% (1)	16% (11)	0	0
Gait disturbance	1% (1)	13% (9)	0	0
Disturbance in attention	3% (2)	7% (5)	0	0
Dyspepsia	3% (2)	7% (5)	0	7% (5)
Nasal congestion	3% (2)	7% (5)	4% (3)	3% (2)
Diarrhea	3% (2)	6% (4)	0	3% (2)
Asthenia	3% (2)	6% (4)	3% (2)	0
Dermatitis	1% (1)	6% (4)	1% (1)	0
Folliculitis	1% (1)	6% (4)	0	1% (1)
Pain in extremity	1% (1)	6% (4)	1% (1)	3% (2)
Delirium	0	6% (4)	0	0

From Study report OV-1022, Tables 22, 23.

Phase II/III controlled Trials

Given that the AE analyses for the Phase II/III trials discussed above displayed risks by dose, I will briefly address dose response in these trials. Dose response can be difficult to interpret in these trials given that patients were titrated to the target dose during the first 3 weeks of the trials and any AEs occurring during titration may have occurred at a dose lower than the subjects' final target dose.

There did appear to be a suggestion of dose response for discontinuations due to AEs in both Phase II/III controlled trials. In OV-1002, 9% of the low dose group and 11% of the high dose group discontinued for AEs. In OV-1012, 7% of the low dose group, 13% of the medium dose group, and 20% of the high dose group discontinued for AEs (placebo 3%). As noted above, there did not appear to be a clear dose response for

overall AEs in trial OV-1002 (low dose 84%, high dose 86%), or OV-1012 (low dose 72%, medium dose 89%, high dose 76%, placebo 68%).

The AE data suggested a potential dose response for the individual AEs of somnolence and constipation. In OV-1002, somnolence occurred in 13% of low dose and 19% of high dose subjects and in OV-1012, somnolence occurred in 12% of placebo subjects, 16% of low dose, 24% of medium dose, and 25% of high dose clobazam subjects. In OV-1002, constipation occurred in 3% of low dose and 8% of high dose subjects and in OV-1012, constipation occurred in 0 placebo subjects, 2% of low dose, 2% of medium dose, and 10% of high dose clobazam subjects.

Concentration Response for Somnolence

Lundbeck examined the relationship between sedation-related AEs (sedation, somnolence, sleepiness, drowsiness, sleepy, lethargy and listless) and concentration of clobazam and/or N-CLB. Using concentration data from OV-1012, Lundbeck used a logistic regression model and in addition to concentration (clobazam and N-CLB separately), they considered demographic and laboratory covariates. Lundbeck reported the following:

Both clobazam dose and clobazam and N-CLB steady-state average concentration were found to positively correlate with the incidence of any sedation-related event during treatment. No covariates were found as explanatory variables. This determination was made taking into account the presence of AEDs, which were allowed in all dose groups in Trial OV-1012.

Lundbeck reported that the median probability of having a sedation-related AE in the lower dose groups (5 and 10mg) was about 10% higher than the placebo group, and for the higher dose groups (20 mg and 40 mg) was about 28% higher than the placebo group (ISS p. 234).

7.5.2 Time Dependency for Adverse Events

In their NDA, Lundbeck provided 2 separate analyses to look at time dependency for AEs (i.e., long term AEs) in clobazam treated patients. To examine onset of AEs, Lundbeck provided AE incidence for different time intervals since starting clobazam. To examine duration of AEs, Lundbeck provided AE prevalence, for different time intervals since starting clobazam. Lundbeck found that for most AEs, the incidence and prevalence were highest during the first time interval. Unfortunately, the first time interval was wide and included study days 1-180.

To further explore time dependency for the early onset AEs, the Division requested that Lundbeck reanalyze the data using the following time intervals: Day 1-7, Day 8-14, Day 15-21, Day 22-35, Day 36-49, Day 50-77, and Day 78-179. The Division requested

these intervals because they corresponded to the study visit days from the controlled LGS trials. Lundbeck provided these analyses in their 6/30/11 submission.

During the first 6 study intervals (through day 77), the overall AE incidence was fairly constant. In the following table, I provide the AE incidences by study interval for AEs that occurred in at least 10% of clobazam study subjects.

Incidence of Treatment Emergent AEs by Time, Phase II/III Clobazam LGS Trials

AE	Study Interval						
	Day 1-7 (n=300)	Day 8-14 (n=295)	Day 15-21 (n=294)	Day 22-35 (N=292)	Day 36-49 (n=281)	Day 50-77 (n=273)	Day 78-179 (n=267)
Any AE	32% (97)	31% (90)	29% (84)	33% (97)	27% (75)	36% (98)	68% (181)
Somnolence	5% (15)	5% (14)	5% (16)	3% (8)	2% (6)	2% (6)	8% (21)
URI	2% (6)	<1% (2)	3% (8)	1% (4)	2% (5)	4% (10)	6% (17)
Pyrexia	1% (4)	1% (4)	2% (5)	2% (7)	<1% (1)	4% (10)	6% (16)
Pneumonia	<1% (1)	<1% (1)	<1% (1)	<1% (2)	<1% (1)	1% (3)	3% (9)
Lethargy	4% (11)	4% (12)	2% (6)	1% (4)	0	<1% (1)	3% (9)
Nasopharyngitis	<1% (2)	1% (3)	2% (5)	2% (5)	<1% (2)	2% (6)	5% (13)
Constipation	<1% (2)	1% (3)	<1% (1)	1% (4)	<1% (2)	1% (3)	2% (6)
Aggression	2% (6)	3% (8)	1% (3)	2% (6)	<1% (2)	2% (4)	3% (7)
Fall	<1% (1)	0	<1% (1)	<1% (2)	0	<1% (2)	4% (11)
Otitis media	<1% (2)	<1% (1)	0	<1% (1)	<1% (1)	2% (5)	5% (12)
Insomnia	<1% (1)	1% (4)	1% (3)	2% (7)	<1% (2)	<1% (4)	3% (7)
UTI	0	0	0	2% (5)	<1% (2)	<1% (2)	2% (6)
Droling	2% (6)	<1% (2)	3% (9)	1% (3)	<1% (2)	2% (4)	2% (6)
Sedation	2% (7)	2% (5)	1% (3)	2% (5)	<1% (1)	<1% (1)	3% (7)
Skin laceration	0	<1% (1)	0	<1% (2)	<1% (2)	<1% (2)	3% (8)

From Table 1, 6/30/11 Submission

In addition to summarizing AE incidence by time intervals, Lundbeck also summarized prevalence of AEs by time intervals. The prevalence of the common AEs generally appeared to increase for the intervals examined during the first 6 months of use.

Prevalence of Treatment Emergent AEs by Time, Phase II/III LGS Clobazam Trials

AE	Study Interval						
	Day 1-7 (n=300)	Day 8-14 (n=295)	Day 15-21 (n=294)	Day 22-35 (N=292)	Day 36-49 (n=281)	Day 50-77 (n=273)	Day 78-179 (n=267)
Any AE	32% (97)	48% (142)	55% (161)	62% (180)	64% (179)	67% (183)	80% (213)
Somnolence	5% (15)	9% (27)	13% (38)	12% (35)	12% (33)	11% (29)	15% (40)
URI	2% (6)	3% (8)	4% (13)	5% (14)	4% (12)	5% (13)	8% (20)
Pyrexia	1% (4)	2% (6)	2% (7)	3% (10)	1% (3)	4% (12)	7% (19)
Pneumonia	<1% (1)	<1% (2)	1% (3)	1% (4)	2% (5)	2% (5)	4% (10)
Lethargy	4% (11)	7% (21)	9% (25)	8% (22)	6% (17)	5% (13)	8% (20)
Nasopharyngitis	<1% (2)	1% (3)	2% (7)	3% (9)	3% (8)	3% (7)	6% (16)
Constipation	<1% (2)	1% (4)	1% (4)	3% (8)	3% (7)	3% (8)	5% (12)

Aggression	2% (6)	4% (12)	4% (13)	6% (18)	5% (15)	6% (16)	6% (16)
Fall	<1% (1)	<1% (1)	<1% (1)	<1% (2)	0	<1% (2)	4% (11)
Otitis media	<1% (2)	1% (3)	<1% (2)	<1% (2)	<1% (2)	2% (6)	5% (14)
Insomnia	<1% (1)	2% (5)	2% (7)	5% (13)	4% (11)	3% (8)	4% (11)
UTI	0	0	0	2% (5)	2% (6)	2% (4)	3% (9)
Drooling	2% (6)	3% (8)	5% (16)	7% (19)	5% (15)	6% (17)	7% (18)
Sedation	2% (7)	4% (11)	3% (10)	5% (13)	4% (11)	4% (12)	6% (15)
Skin laceration	0	<1% (1)	<1% (1)	1% (3)	2% (5)	2% (4)	4% (11)

From Table 2, 6/30/11 Submission

7.5.3 Drug-Demographic Interactions

Lundbeck provided AE analyses that looked for potential drug-demographic interactions (age, sex, race, and region). Lundbeck performed these analyses by calculating AE risks (those occurring in at least 10% of all clobazam subjects) stratified by the demographic variable of interest. Lundbeck's analyses include pooled data from all Phase II/III trials (controlled and open label) and include no untreated comparator group. The lack of a comparator group limits interpretability of these analyses because one cannot determine if observed differences in risk are due to drug-demographic variable interaction, or merely represent the differences due to the demographic variable that one would observe in the absence of drug. Only one controlled trial (OV-1012) included a placebo group. It would not have been possible to conduct meaningful stratified analyses using only OV-1012 trial data because based on the relatively small number of subjects and AEs, many strata would have included few/no events. I summarize Lundbeck's drug-demographic analyses in the following paragraphs.

Age

Lundbeck summarized AE data, stratifying by patient age. Lundbeck used the following age categories: 2-11 years, 12-16 years, and >16 years (Lundbeck did not include the data for the 1 patient who was <2 years old). Lundbeck commented that pyrexia, otitis media, pneumonia, and upper respiratory tract infections decreased in frequency with increasing age while drooling, urinary tract infection and skin laceration increased with increasing age. I summarize that information below.

Treatment Emergent AEs that Occurred in at least 10% of Clobazam subjects, Stratified by Age

	Clobazam Subjects		
	2-11 years (n=192)	12-16 years (n=51)	>16 years (n=56)
All AEs	93% (178)	86% (44)	96% (54)
Constipation	14% (26)	14% (7)	14% (8)
Pyrexia	24% (46)	16% (8)	5% (3)
Nasopharyngitis	13% (25)	20% (10)	13% (7)
Otitis media	18% (34)	8% (4)	0

Pneumonia	17% (33)	14% (7)	4% (2)
Upper respiratory tract infection	31% (59)	14% (7)	11% (6)
Urinary tract infection	9% (18)	14% (7)	14% (8)
Fall	11% (21)	16% (8)	18% (10)
Skin laceration	7% (14)	14% (7)	16% (9)
Drooling	9% (17)	12% (6)	16% (9)
Lethargy	10% (19)	26% (13)	20% (11)
Sedation	9% (17)	8% (4)	16% (9)
Somnolence	24% (46)	24% (12)	30% (17)
Aggression	11% (21)	10% (5)	23% (13)
Insomnia	12% (23)	12% (6)	11% (6)

From 120 Day Safety Update Table 32, p.72

Sex

Lundbeck reported that when stratified by sex, urinary tract infections occurred more commonly in females and insomnia in males. I summarize the AE by sex risks in the following table.

Treatment Emergent AEs that Occurred in at least 10% of Clobazam subjects, Stratified by Sex

	Clobazam Subjects	
	Female (n=119)	Male (n=181)
Any AE	94% (112)	91% (165)
Constipation	13% (16)	14% (25)
Pyrexia	13% (15)	24% (43)
Nasopharyngitis	13% (16)	15% (27)
Otitis media	10% (12)	15% (27)
Pneumonia	16% (19)	14% (25)
Upper respiratory tract infection	26% (31)	23% (42)
Urinary tract infection	19% (23)	6% (11)
Fall	13% (16)	13% (23)
Skin laceration	7% (8)	12% (22)
Drooling	10% (12)	11% (20)
Lethargy	16% (19)	13% (24)
Sedation	13% (15)	8% (15)
Somnolence	24% (29)	26% (47)
Aggression	10% (12)	16% (28)
Insomnia	7% (8)	15% (27)

From 120 Day Safety Update Table 35, p.76

Race

Lundbeck summarized AEs stratified by the following 3 race categories: White, Asian, and other. Lundbeck noted that Asians tended to have the lowest AE risks but this may represent cultural rather than biological differences. I summarize those data below.

Treatment Emergent AEs that Occurred in at least 10% of Clobazam subjects, Stratified by Race

	Clobazam Subjects		
	White (n=202)	Asian (n=60)	Other (n=38)
All AEs	97% (196)	73% (44)	97% (37)
Constipation	15% (31)	7% (4)	16% (6)
Pyrexia	16% (32)	25% (15)	29% (11)
Nasopharyngitis	11% (23)	15% (9)	29% (11)
Otitis media	15% (30)	0	24% (9)
Pneumonia	16% (32)	8% (5)	18% (17)
Upper respiratory tract infection	24% (49)	17% (10)	37% (14)
Urinary tract infection	14% (28)	5% (3)	8% (3)
Fall	16% (32)	5% (3)	11% (4)
Skin laceration	13% (26)	2% (1)	8% (3)
Drooling	12% (25)	8% (5)	5% (2)
Lethargy	17% (35)	0	21% (8)
Sedation	12% (25)	3% (2)	8% (3)
Somnolence	29% (58)	12% (7)	29% (11)
Aggression	16% (33)	3% (2)	13% (5)
Insomnia	14% (29)	3% (2)	11% (4)

From 120 Day Safety Update Table 38, p.79

Region

Lundbeck summarized AEs stratified by the following 3 trial site regions: United States, Rest of World, and India. Lundbeck noted that subjects from the US tended to have the highest AE risks but commented that this may represent cultural rather than biological differences. I summarize those data below.

Treatment Emergent AEs that Occurred in at least 10% of Clobazam subjects, Stratified by Region

	Clobazam Subjects		
	US (n=230)	Rest of World (n=17)	India (n=53)
All AEs	98% (226)	82% (14)	70% (37)
Constipation	17% (39)	0	4% (2)
Pyrexia	19% (44)	6% (1)	25% (13)
Nasopharyngitis	15% (34)	6% (1)	15% (8)
Otitis media	17% (39)	0	0

Pneumonia	17% (39)	6% (1)	8% (4)
Upper respiratory tract infection	29% (66)	0	13% (7)
Urinary tract infection	14% (31)	0	6% (3)
Fall	16% (37)	0	4% (2)
Skin laceration	13% (30)	0	0
Drooling	12% (28)	0	8% (4)
Lethargy	19% (43)	0	0
Sedation	13% (29)	0	2% (1)
Somnolence	28% (64)	29% (5)	13% (7)
Aggression	16% (37)	12% (2)	2% (1)
Insomnia	15% (35)	0	0

From 120 Day Safety Update Table 41, p.83

7.5.4 Drug-Disease Interactions

Lundbeck addressed drug-disease interactions by summarizing data from their own Phase I trial in patients with renal impairment, and a Phase I trial in patients with hepatic impairment that was published in the medical literature.

Lundbeck noted that in trial OV-1032, they administered clobazam single 20mg and multiple 20mg (every day for 7 days) doses to healthy subjects and to patients with mild and moderate renal impairment. Lundbeck noted that there were no deaths, SAEs, AEs resulting in withdrawal, and no clinically important physical exam, vital sign, laboratory, or ECG findings. All subjects experienced at least 1 AE (with the exception of 1 moderate somnolence AE, all AEs were categorized as mild by the investigators). Lundbeck noted that there were minor differences in clobazam and N-CLB exposure for healthy subjects compared to those with moderate renal impairment but commented that no dose adjustment is required for patients with mild or moderate renal impairment (ISS, p.246).

In a published trial, Monjanel-Mouterde et al administered a single 20mg dose of clobazam to 6 healthy males, 6 subjects (3 male, 3 female) with acute viral or toxic hepatitis (all with jaundice but not acute liver failure), and 9 subjects (4 male, 5 female) with alcoholic or post hepatic cirrhosis. Using Child-Pugh classification, 5 of these subjects had mild or moderate cirrhosis and 4 had severe cirrhosis. Lundbeck noted that the C_{max} of clobazam was decreased by 32% in patients with liver disease, but the difference in C_{max} for N-CLB was not significant between groups. The T_{max} for N-CLB was prolonged in liver disease patients. Lundbeck explained that the authors fitted clobazam pharmacokinetics to a two compartment model and performed a computer simulation for the three typical subjects from each group using 3 therapeutic regimens: 10 mg BID, 20 mg QD and 20 mg BID for 20 days. The authors found that regardless of the regimen, plasma clobazam concentrations were the same in all subjects, supporting that liver impairment did not alter the total CL, and suggesting that clobazam

accumulation should not occur in liver impairment. Lundbeck recommended that clobazam doses should be titrated upward cautiously to effect and tolerability in patients with liver dysfunction.

7.5.5 Drug-Drug Interactions

Lundbeck's exploration for drug-drug interactions for clobazam included analyses of select Phase I trials, and review of population PK modeling data. Lundbeck reported their findings by summarizing data pertinent to specific cytochrome P450 isoform and the effect of the coadministered drug(s) (induction vs. inhibition). Lundbeck first looked at the effect of other drugs on clobazam and N-CLB, and then looked at the effect of clobazam on other drugs. Lundbeck also reviewed interaction data for Valproic acid and lamotrigine.

Lundbeck reported that in humans, CYP3A4/5 is primarily responsible for metabolizing clobazam to N-CLB, but that CYP2C19 and CYP2B6 also have the potential to metabolize clobazam. Biotransformation of N-CLB to 4'-hydroxy-N-CLB is primarily mediated by CYP2C19 (Non-Clinical Overview, p.16).

Phase I Trials

OV-1021 examined the effect of multiple doses of ketoconazole or omeprazole on the single dose PK profile of clobazam. Subjects were administered a single dose of clobazam on day 1, followed by either ketoconazole 400mg QD or omeprazole 40mg QD on Days 17-22, with a single dose of clobazam also administered in Day 22. Lundbeck performed baseline CYP2C19 genotyping on all patients.

OV-1023 examined the effect of clobazam on the PK of midazolam, caffeine, tolbutamide, and dextromethorphan (administered as a drug cocktail). Investigators administered a single oral dose of the drug cocktail on Day 1 followed by clobazam 40mg QD on Days 4-19, with the drug cocktail coadministered on Day 19. Lundbeck performed baseline CYP2C19 and CYP2D6 genotyping on all patients.

Population PK Data

Lundbeck used concentration data from OV-1012 and OV-1017 to characterize the effect of the presence of AEDs on PK on clobazam and N-CLB. Lundbeck looked at the following groupings of AEDs: CYP3A4 inducers (phenobarbital, phenytoin, carbamazepine, n=77), CYP2C19 inducers (valproic acid, phenobarbital, phenytoin, carbamazepine, n=18), and CYP2C19 inhibitors (felbamate, oxcarbazepine, n=17).

CYP3A4 Inhibition on Clobazam and N-CLB

Based on results from Trial OV-1021, Lundbeck concluded that co-administration of the CYP3A4 inhibitor, ketoconazole, did not have an effect on plasma concentrations of clobazam or N-CLB that would require clobazam dose adjustment. Specifically,

Lundbeck reported that coadministration of ketoconazole resulted in 53% and 54% increases in clobazam AUC from zero to infinity (AUC_{0-inf}) and area under the curve from zero to last quantifiable concentration (AUC_{0-lqc}) values, respectively, and a 15% decrease in clobazam C_{max} relative to administration of clobazam alone. Clobazam apparent plasma clearance was decreased 3%. For N-CLB, coadministration of ketoconazole and clobazam resulted in 18% and 15% increases in AUC_{0-inf} and AUC_{0-lqc} , respectively and a 1% decrease in C_{max} relative to clobazam alone (ISS, p.249).

CYP3A4 Induction on Clobazam and N-CLB

Based on results of their population PK modeling, Lundbeck concluded that the effect of coadministration of CYP-3A4 inducers on clobazam was negligible and did not support the need for clobazam dose adjustment (ISS, p.249).

CYP2C19 Inhibition on Clobazam and N-CLB

Based on results from Trial OV-1021, Lundbeck concluded that co-administration of the CYP2C19 inhibitor, omeprazole, did not have an effect on plasma concentrations of clobazam or N-CLB that would require clobazam dose adjustment. Lundbeck did note that with “the rapid absorption and short elimination half-life of omeprazole and slow formation of N-CLB from clobazam, the effect on N-CLB in this trial may not be predictive of the extent of the effect (ie, may be greater than) on N-CLB at steady-state.” (IS, p.249)

Effect of Clobazam on CYP1A2 Substrates

Lundbeck reported no meaningful differences for caffeine or 1,7-paraxanthine (main metabolite of caffeine), AUC or C_{max} when comparing drug cocktail alone to co administration of clobazam and drug cocktail (ISS, p.250).

Effect of Clobazam on CYP2C9 Substrates

Lundbeck found no meaningful differences for AUC or C_{max} for tolbutamide, 4-hydroxytolbutamide, or carboxytolbutamide when comparing drug cocktail alone to co administration of clobazam and drug cocktail (ISS, p.250).

Effect of Clobazam on CYP2D6 Substrates

Lundbeck noted that concomitant use of clobazam with drugs metabolized by CYP2D6 may require lower doses for those other drugs. Lundbeck’s statement was based on the finding that with co administration of clobazam, dextromethorphan AUC increased 90-95% and C_{max} increased 59%, consistent with weak inhibition of CYP2D6 (ISS, p.250).

Effect of Clobazam on CYP3A4 Substrates

Lundbeck reported non clinically meaningful decreases of 27% and 24% for AUC and C_{max} of midazolam and a 4-fold increase in AUC and a 2-fold increase in C_{max} for 1-hydroxymidazolam when co administered with clobazam. Lundbeck noted that these findings were consistent with mild induction of CYP-3A4 and subsequent decreased elimination of 1-hydroxymidazolam (ISS, p.251).

Effect of Clobazam on Valproic acid and Lamotrigine

Using population PK data, Lundbeck determined that there was no significant effect of clobazam or N-CLB on concentrations of valproic acid or lamotrigine (ISS, p.251).

CYP2C19 Genotypes

Data from Phase I clinical trials, population PK analyses and published trials estimated that CYP2C19 PMs have 3 fold to 6-7 fold higher exposure to N-CLB compared to IM/EM or EM exposed individuals (ISS, p.252). Lundbeck noted that PMs treated with 40mg/day (labeling recommended dose) had exposures similar to EMs dosed at 120mg to 160mg/day (ISS, p.252).

Lundbeck performed CYP2C19 genotyping in the Phase I trials OV-1021, OV-1022, OV-1023, OV-1032, and OV-1038; and in the Phase II/III trials OV-1002 and OV-1012 (US sites only). Lundbeck identified 13 subjects (6 from Phase I trials and 7 from Phase II/III trials) as CYP2C19 poor metabolizers.

None of the Phase I clobazam PMs experienced an SAE and none discontinued for an AE. Lundbeck summarized data for the 3 PM subjects from Phase I trials who were exposed to supratherapeutic doses of clobazam (total daily doses of 120mg n=1, and 160mg n=2). One subject in trial OV-1038 (0001-2003) dosed at 120 mg/day to steady state had a moderate AE of delirium. N-CLB concentrations were approximately 13- to 15-fold ($AUC_{0-\tau}$ 309500 ng*hr/mL) higher in this subject compared with intermediate or extensive metabolizers receiving 40 mg/day. Lundbeck commented that similar high exposures are not expected in PMs dosed at the labeling recommended clobazam doses. Subjects 0001-1025 and 0001-1088 both dosed at 160mg/day experienced dizziness and somnolence. The remaining PMs from the Phase I studies received doses of 20mg (n=1) and 40mg/day (n=2) and had AEs similar to those seen in the rest of the Phase I population.

In the LGS trials, 1 subject from OV-1002 (0003-0104) and 6 subjects from OV-1012 (0027-7029, 0038-7060, 0817-7088, 0012-8019, 0035-8036, and 0050-8053) were PMs. Three of the subjects were in the low dose group and 4 were in the high dose group during the RCT. None of these patients died and 3 experienced one or more SAEs. These SAEs included pneumonia (2 subjects), failure to thrive, influenza, respiratory distress, and seizures. One additional PM LGS subject experienced pneumonia that was not an SAE. None of the subjects discontinued for an AE and all except subject 0050-8053 continued into the open label study and had clobazam exposures >1 year. Subject 0050-8053 discontinued from OV-1012 because his parents withdrew consent.

In addition to concerns about exposure in genotypic poor metabolizers, one must also be concerned about exposure in patients who are receiving drugs that inhibit CYP2C19. As noted above, based on results from OV-1021 which administered clobazam and

omeprazole, Lundbeck did not feel that dose adjustment was needed with CYP2C19 inhibitors. Lundbeck also recognized that with the rapid absorption and short elimination half-life of omeprazole and slow formation of N-CLB from clobazam, the effect on N-CLB in this trial may not be predictive of the extent of the effect (ie, may be greater than) on N-CLB at steady-state.

Using the FDA Drug Development Resources web site, I identified strong CYP2C19 inhibitors (\geq 5-fold increase in AUC or $>80\%$ decrease in CL).³ This table identified fluconazole, fluvoxamine, and ticlopidine as strong inhibitors. Using the sponsor's NDA concomitant medication data set, I identified subjects from the Lundbeck trials who were taking these medications. Ten patients were administered fluconazole, 1 subject received fluvoxamine, and no patients received concomitant ticlopidine. I then used the sponsor's NDA AE data set to identify all AEs reported during the time that fluconazole and clobazam were coadministered.

Most patients who received clobazam and a strong CYP2C19 inhibitor concomitantly either experienced no AEs during the period of coadministration or experienced AEs that appeared to be related to the underlying condition at the time of coadministration (ex., candidiasis, sepsis, dermatitis, etc.). Three cases were suggestive of a possible interaction. Subject OV-1012-0822-7079 was randomized to the 0.5mg/kg/day dose of clobazam in study OV-1012. This subject was taking fluvoxamine upon entry into the study. This subject experienced a somnolence AE that led to discontinuation from the study. Subject OV-1012-0012-8031 experienced a non serious AE of somnolence that occurred during the period of coadministration of clobazam and fluconazole and that apparently ended when fluconazole was stopped. Subject OV-1002-0012-0107 was receiving clobazam 15mg/daily and on study day 135 was prescribed fluconazole for the treatment of airway congestion and thrush. On study day 144, the subject experienced sedation and floppiness and was hospitalized. Fluconazole was stopped and clobazam was temporarily held and lamotrigine dose was reduced. The subject recovered from this event and continued in the study.

Discussion

Clobazam's active metabolite N-CLB is metabolized by CYP2C19 and poor metabolizers have roughly 5-fold higher exposures to N-CLB than intermediate or extensive metabolizers. Lundbeck included genotyping in their clinical trials but this information was not used to inform dosing decisions. Lundbeck identified 13 poor metabolizers in their studies. These PM subjects did not appear to experience increased toxicity as evidenced by AEs. Lundbeck feels that the dose titration recommendations in labeling obviate the need for genotyping patients prior to treatment. Lundbeck's proposal seems reasonable, although the experience in PMs in

3 Table 5. Classification of In Vivo Inhibitors of CYP Enzymes(1)
(7/28/2011)<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm>

the clinical trials was limited. A related concern involves patients taking clobazam who are started on a drug that inhibits CYP2C19. This combination could result in elevated exposures to N-CLB and risk for AEs. The Division should consider labeling language to alert prescribers about the potential for AEs related to concomitant use of clobazam with CYP2C19 inhibitors.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

As explained above, Lundbeck designated cancer-related AEs as events of special interest. Clinical trials cancer-related AEs were reviewed with other events of special interest above, in section 7.3.4. Post-marketing cancer-related AEs are reviewed with other post-marketing AEs of special interest below, in section 8.

7.6.2 Human Reproduction and Pregnancy Data

Lundbeck proposes that clobazam be classified as Pregnancy class C, noting that reproductive toxicity studies demonstrate adverse effects on fetal development but that there are no data from adequate and well controlled trials in humans or reliable post marketing data that allow an evaluation of the effects of clobazam on reproduction and fetal development. Lundbeck feels that clobazam (b) (4)

Lundbek acknowledges that administration of high doses of clobazam immediately prior to or during childbirth can result in the “floppy baby syndrome”, manifested by hypothermia, hypotonia, respiratory depression, and difficulty feeding. In addition, Lundbeck notes that infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period.

Lundbeck summarized pregnancy exposures from the clobazam development program, spontaneous post-marketing reports, and the medical literature. Lundbeck’s summary includes reports of spontaneous abortions, congenital malformations and postnatal adverse events (respiratory depression, hypotonia, difficulty feeding, etc.). In many cases, the exposure to clobazam occurred along with exposure to other drugs, making assessment of the role of clobazam difficult. In cases where clobazam was the only reported drug, the reports generally included limited information complicating the assessment of the role of clobazam. I summarize information about pregnancy exposures to clobazam below.

Lundbeck noted that there were no pregnancies in their clinical trials or the Legacy Epilepsy trial 301. Investigators reported pregnancy exposures in the Legacy Psychiatry trials but the study reports provided no information about these events.

To identify post-marketing cases of pregnancy exposure to clobazam, Lundbeck searched their database for coded terms related to pregnancy and used a text string search of the narrative section to identify the words pregnancy and pregnant. In their ISS submission, Lundbeck identified 131 post-marketing reports using their search strategy. Lundbeck determined that 5 cases did not describe the drug exposure during pregnancy and therefore Lundbeck did not consider these cases in their analyses. Among the remaining 126 reports, 24 did not include sufficient information for analysis. Seventy-six reports (73 unique cases) noted exposure to multiple antiepileptic drugs. Lundbeck identified 24 reports (21 unique cases) where clobazam was the only or the primary suspect drug identified by the reporter. For 6 of these cases, the reports noted normal deliveries and 3 did not include information about outcome. I summarize information from the 12 remaining unique cases in the following table.

Summary of Selected Pregnancy Exposure to Clobazam Cases

Case #	Exposure	Outcome
DKLU1048235	2-3 doses, week 36	Birth at 37 weeks, hypertrophic cardiomyopathy
DKLU1059920	Started 2 years prior to pregnancy	Bilateral talipes on 21 week u/s. No pregnancy outcome information
DKLU1057819	Started prior to pregnancy	Birth at week 39, 3400g, male, APGAR 1min 5, 5 min 7, age 3 had speech disorder
DKLU1048763	Started prior to pregnancy	Pregnancy complicated by nausea, fatigue; Premature birth 740g; diaphragmatic hernia; death
DKLU1051890	Started prior to pregnancy	Spontaneous abortion week 10
DKLU1059728	First 3 weeks	Spontaneous abortion week 7
DKLU1047818	Clobazam, tegretol, and sabril started prior to pregnancy	Spontaneous abortion month 3
DKLU1051611	Throughout pregnancy	No congenital abnormalities, infant drowsy, poor weight gain; declining blood levels of N-CLB after birth (151ug/mL at 1 month), recovered
DKLU1055428	Throughout pregnancy	C-section week 36 for fetal bradycardia, transient tachypnea of newborn, drug withdrawal, outcome not reported
DKLU1055302	Started month 6; with heptaminol	"a-reactive" requiring feeds by gavage for 3 weeks; recovered
DKLU1049018	Throughout pregnancy	Hypotonia, irritability
DKLU1058370	Clobazam and lamotrigine (dates N/R)	Feeding problems, hypotonia

From ISS, pp.253-5.

In the 120 day Safety Update, Lundbeck identified 7 additional reports of clobazam exposure during pregnancy. Two cases were reported in a literature abstract and described 2 infants (one with concomitant carbamazepine, the other with concomitant phenytoin pregnancy exposure) who were exposed to clobazam throughout pregnancy and were born with limb reduction defects. Three cases were reported from New Zealand. One report described an infant with neonatal respiratory failure, low birth weight, and GERD. A second report described an infant with neonatal respiratory failure, low birth weight, GERD, increased heart rate, and absent tooth enamel. The third report described an infant with neonatal respiratory failure, low birth weight, GERD, and difficulty gaining weight. The final 2 new reports described infants with pregnancy exposure to multiple drugs. One infant exposed to clobazam, valproic acid, ciprofloxacin, levetiracetam, and doxylamine was determined to have absence of the external auditory meatus and hyperechogenicity of the kidneys on a 20 week ultrasound and postnatal assessment determined the infant had hearing impairment. Results of the genetic assessment, bone series, and renal ultrasound were not available. The final new report described an infant exposed to clobazam, which was discontinued at the beginning of pregnancy, and valproate and lamotrigine, which were continued throughout the pregnancy, who subsequently gave birth at term to infant with ear malformation, 'open wound of internal structures of mouth'; deafness, and speech disorder (120 Day Safety Update, pp.94-95).

Lundbeck also searched the medical literature for publications describing pregnancy exposures to clobazam. I summarize those results below.

In a publication by Buchanan, the author reported the results of an open-label, uncontrolled study. The author noted that 3 subjects took clobazam throughout their pregnancies. Two of these patients had normal infants. The remaining subject had a child with no dysmorphic features but who exhibited persistent pulmonary hypertension of the newborn and later showed features of attention deficit disorder.

Lundbeck identified 2 trials where clobazam was administered in the final trimester of pregnancy. Baudet, et al. conducted a randomized, double blind, placebo controlled trial of clobazam 15 mg (5 mg TID dosing) administered for anxiety in 17 women in their final 3 months of pregnancy. One clobazam subject discontinued due to cesarean section for placenta previa. At birth, the delivery dates, delivery weights, and Apgar scores were identical in the two groups, the deliveries were without complication, and anomalies were not observed.

Nandakumaran et al. investigated maternal-fetal transfer of clobazam in a clinical trial. Subjects in the clinical trial of clobazam were 35 women in labor and clobazam was administered as an anxiolytic at a single oral dose of 20 mg. Twenty-one (21) newborns were monitored at birth and on day 5 for clinical signs, and were compared to a control group of 9 infants born to mothers without administration of drug. Drug concentrations in

maternal vein and umbilical arterial and mixed venous bloods were determined at delivery. The drug appeared in the umbilical venous and arterial circulation simultaneously with its appearance in the maternal blood, and near similar levels was found in mother and fetus during the interval studied. At delivery, clobazam was detected in the umbilical blood of 16 out of 19 newborns, with levels ranging from 16 ng/mL to 335 ng/mL (mean 39.6 +/- 1.5 SEM) and on day 5 was detected in 9 of 14 infants, with a range of 20 ng/mL to 100 ng/mL (missing data not explained). Four infants with positive clobazam levels at delivery had no detectable levels on day 5. One infant exhibited breathing difficulty; however, there was no detectable clobazam level in an umbilical sample 40 minutes following drug administration, or on day 5 in this infant. All other clinical measurements in all infants, including heart rate, neurological symptoms and APGAR scores, showed no statistical difference between test and control groups. The authors concluded that the presence of breathing difficulty in one infant exposed to clobazam, although not correlated with blood levels of clobazam, does not preclude caution with the use of clobazam perinatally.

Lundbeck identified 2 publications describing 3 pregnancies with multiple drug exposures (including clobazam). Lanza et al. described a 26-year-old female who received valproate and clobazam and delivered a 3210 g infant, Apgar score of 6-9, with hypothermia, cyanosis, and trembling. Cissoko et al. reported 2 cases: a 20-year-old female who received vigabatrin, carbamazepine, and clobazam during her pregnancy and had a full-term infant (Apgar 10, weight 3030 g) with no malformations or disorders; and a 27-year-old female who received lamotrigine and clobazam throughout her pregnancy and had a premature infant (35 weeks; weight 2580 g) with Apgar scores of 4/8/10, no malformations, but transient respiratory distress, and thrombocytopenia.

Robert et al. reported no malformations in infants delivered by females with epilepsy in connection with clobazam use in combination with valproic acid (2 patients) and phenobarbitone and carbamazepine (one patient) during the first trimester of pregnancy.

McElhatton reported that an infant exposed to clobazam in utero in a 2-year follow-up study experienced withdrawal syndrome with time of onset of withdrawal 24 to 48 hours that lasted up to 2 weeks.

In a review titled Anticonvulsant use during lactation, Hagg and Spigset explained that after short-term administration, clobazam and its active metabolite N-CLB are transferred into breast milk in small quantities. The authors noted that the elimination half-lives are approximately 24 hours for the parent compound and 40 hours for the metabolite and that infant exposure is expected to be slightly higher after multiple doses. The authors concluded that an infant would receive, at most, 10% of the usual therapeutic pediatric dosage of 0.5 mg/kg/day used in the treatment of seizures (ISS, pp. 255-6).

7.6.3 Pediatrics and Assessment of Effects on Growth

Lundbeck provided summarized height and weight changes in the controlled LGS trials (ISS Table 78, p.170) but these data are not of value in determining if clobazam has an effect on growth. The height data were neither collected uniformly, nor using precise methodology. The protocols for these trials only required height measurements at Day-1, and so there are available mean changes for only a subset of patients (presumably where investigators captured final height data despite the lack of a protocol requirement). Heights in these trials were measured without shoes but there was no requirement for the use of a stadiometer. Even if height data were collected more systematically and accurately, the relatively short duration of the clinical trials and questions about the validity of using population based data for growth comparisons (Z-scores) would preclude any conclusions about clobazam's effect on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

To identify clobazam overdose events in the clinical trials, Lundbeck performed a text string search for the following terms “*overdos*”, “*error*”, “*toxic*”, and “*administ*”. This search identified 5 cases of overdoses with clobazam. Three cases were from the Lundbeck LGS trials OV-1012 (n=1) and OV-1004 (n=2). In these 3 cases, the caregivers administered incorrect, higher doses of clobazam than were assigned (one case not specified, one case 50mg BID instead of 10mg BID and one case 40mg BID instead of 20mg BID). One patient was hospitalized for somnolence, restlessness, walking difficulties and falling. In all cases, the events resolved and the patients continued in the trials. Lundbeck identified the 2 remaining clinical trials overdose cases from the legacy trials. One case was described as an accidental overdose and for the other case, there was insufficient information to determine if the case was accidental or intentional. Neither case was classified as an SAE.

Lundbeck summarized post-marketing reports of overdose. In the NDA, Lundbeck described 39 reports (42 cases) where reporters identified clobazam as the suspect product in an overdose or described elevated blood levels of clobazam or N-CLB.

In the NDA, Lundbeck reported 4 post marketing overdose cases had death as an outcome. Lundbeck reported no additional fatal overdose cases in the 120 Day Safety Update. One of the fatal cases was reported in a publication that reviewed benzodiazepine use in Britain from 1980-89. The publication included limited information about the circumstances surrounding the event. A second fatal case was reported in the literature and described a patient with underlying liver, pulmonary, and renal abnormalities and a history of alcoholism and psychiatric disease. She was found dead and had vomited. She had a postmortem blood concentration of clobazam of 3.9ug/mL and N-CLB was detected but not quantified. The 2 remaining fatal overdose

cases were spontaneously reported. The first was an infant with multiple hospitalizations for refractory seizures/status epilepticus. The patient experienced somnolence, hypotonia, pulmonary congestion and was hospitalized. She was diagnosed as an overdose case. She was receiving clobazam 20mg daily (prescribed dose not reported). She died but the cause of death was not reported. In the last fatal case, a 68 year old female patient died from aspiration/pneumonia 1 month after an intentional clobazam overdose (80 tablets). She was hospitalized and clobazam level was reportedly at the maximum of normal range.

For the non-fatal overdose cases that included dose, the highest reported clobazam dose ingested was 240mg. The AEs reported in overdose cases included coma, somnolence/sedation, gait disturbance, nausea, asthenia, ataxia, bradycardia, decreased appetite, fatigue, hyperkinesia, hypotonia, and vertigo. Lundbeck noted that for the majority of overdose cases AEs were classified as mild or moderate and did not require intensive care (ISS, p.259). In the 120 Day Safety Update, Lundbeck reported 4 additional non fatal overdose cases. One case was a multidrug (clobazam, phenytoin) and alcohol ingestion and the patient was treated in the ICU with flumazenil, activated charcoal, and hemodialysis, and improved. The 3 remaining cases included 2 accidental ingestions and one intentional ingestion (8 tablets). All three of these patients recovered without medical intervention (120 Day Safety Update, p.96).

Drug Abuse Potential

Clobazam is a 1,5 benzodiazepine that had been classified as Schedule IV by the Drug Enforcement Administration since 1984. Lundbeck agrees with clobazam's current schedule and therefore has submitted no formal clinical abuse liability studies.

Lundbeck explained that the complex synthesis of clobazam would make it unlikely that it could be synthesized by street chemists. Clobazam tablets could be crushed for inhalation but since clobazam is not water soluble it would be difficult for abusers to make an injectable form.

An abuse study in monkeys found that clobazam was not self-administered as a substitute for morphine nor was there evidence of habituation.

Lundbeck provided some background data on abuse of benzodiazepines. The anxiolytic properties of benzodiazepines may lead to dependence and abuse. Lundbeck noted that the June 2009 National Institute on Drug Abuse Report of the Community Epidemiology Working group found that alprazolam, clonazepam, and diazepam were the most frequently reported benzodiazepines identified by forensic labs. Six of the 12 areas with Drug Abuse Warning Network data had increases in estimated emergency department visits involving nonmedical use of benzodiazepines from 2003-2007. Lundbeck reported that polydrug abusers, patients with a history of alcohol abuse, and the elderly are at greater risk for benzodiazepine abuse/misuse. Benzodiazepines are rarely the preferred sole drug of abuse with 80% of benzodiazepine abuse being part of

polydrug use. Because of rapid onset, short half-life and high lipophilic properties, alprazolam and lorazepam are the benzodiazepines most likely to be abused. Lundbeck feels that given the proposed indication for clobazam, it will not be widely prescribed and therefore not as available for abuse (ISS, p.261).

Lundbeck briefly reviewed potential abuse potential AE terms in the clobazam development program. To search for abuse potential AEs, Lundbeck searched for the following terms/text strings:

Abdominal pain, Agitation, Anxiety, Confusional state, *convulsion*, *seizure*, Delirium, Depersonalisation, Derealisation, *diarrhoea*, Convulsion, Agitation, *hallucinat*, Headache, Hyperacusis, Photophobia, Allodynia, Hyperpathia, Sensory disturbance, Abnormal dreams, *insomnia*, Irritability, Mental impairment, Myalgia, Nervousness, Hypoaesthesia, Palpitation*, Paresthesia, Restlessness, *sleep* Disorder, Hyperhidrosis, Psychotic disorder, *psychos**psychot*, Tension, Tremor, *Withdraw*

Lundbeck noted that somnolence, aggression, and sedation were commonly reported in the Phase II/III LGS trials and Legacy trial 310. Lundbeck noted that it is difficult to distinguish the abuse potential with clobazam based on these terms given the prevalence of such events in the population studied (ISS, p.262).

Post marketing abuse reports

Using the same list of terms/text strings listed above, Lundbeck searched the post marketing report database to identify abuse potential AEs. The search identified 412 unique cases. Dizziness was the most commonly identified term (n=69) followed by agitation (n=59), somnolence (n=55), aggression (n=51), confusional state (n=39), irritability (n=32), memory impairment (n=25), amnesia (n=18), feeling abnormal (n=18), and disturbance in attention (n=14). No other abuse potential terms were reported more than 10 times. Lundbeck concluded that “Since many of these AEs are expected within the patient population under study and given the nature of benzodiazepines, it is difficult to distinguish a true abuse potential correlation with clobazam.” (ISS, p.263).

At the request of the Controlled Substance Staff, the Office of Surveillance and Epidemiology searched the AERS and WHO Vigibase databases for cases of misuse, abuse, and overdose with clobazam. OSE identified few cases. OSE concluded that “there does not appear to be overwhelming evidence of abuse, misuse, or overdose with clobazam.” (OSE memo dated 8/2/11)

Withdrawal and Rebound

Abrupt discontinuation of benzodiazepines can result in withdrawal symptoms. Lundbeck captured withdrawal-related AEs from the 4 multi-dose Phase I trials where clobazam was abruptly stopped without tapering (subjects were followed for 30 days after last clobazam dose) and from the Phase II/III LGS trials, where subjects who discontinued were tapered off clobazam.

In the multidose Phase I trials and the Phase II/III LGS trials, if a subject experienced a withdrawal-related AE after stopping clobazam, and the investigator recognized that event as a withdrawal symptom, the investigator captured the event on the CRF and wrote a narrative. The withdrawal-related High level terms and AE preferred terms considered by investigators were:

High Level terms: Delusional disorders, Memory loss (excl dementia), Cognitive and attention disorders and disturbances NEC, Psychotic disorder NEC, Perception disturbances, Thinking disturbances, Communication disorders, Sensory abnormalities NEC, Mood disorders NEC, and Emotional and mood disturbances NEC

Preferred terms: Euphoric mood, Agitation, Feeling abnormal, Poisoning, Sedation, Feeling of relaxation, Inappropriate affect, Dizziness, Thinking abnormal, Illusion, Flashback, Inappropriate affect, Somnolence, Sluggishness, Somnolence, Stupor, Depersonalisation, Psychomotor hyperactivity

In the 4 included Phase I trials, 68 of the 207 enrolled subjects experienced a total of 193 withdrawal-related AEs. The majority of these events were reported within the first 7 days after stopping clobazam. The risk for reporting withdrawal symptoms appeared to increase with the clobazam dose at the time of discontinuation. The following table summarizes the number of subjects and the number of withdrawal-related AEs from the 4 Phase I trials.

Summary of Potential Withdrawal-related AEs from 4 Phase I Clobazam Trials

Trial	Number of Clobazam subjects	Max total daily dose at end of Trial	Duration	Potential Withdrawal-Related AEs after stopping clobazam	
				Subjects % (n)	Events n
OV-1022	70	40mg	21 days	33% (23)	90
	70	160mg	29 days	41% (29)	75
OV-1023	18	40mg	16 days	22% (4)	8
OV-1032	25	20mg	8 days	8% (2)	2
OV-1038	12	120mg	39 days	42% (5)	9
	12	160mg	34 days	42% (5)	9
Total	207*			68	193

From ISS Table 108, p.267

The most commonly reported withdrawal AEs were headache, insomnia, anxiety, tremor, palpitations, hyperhidrosis, irritability, decreased appetite, diarrhea, and visual impairment/vision blurred. Some subjects were treated for withdrawal with concomitant medications. Concomitant medication such as diazepam and/or lorazepam were given for 72 of the 193 reported AEs, while other concomitant medications (including Tylenol,

propranolol, Imodium, or a sleep aid) were given for 15 of the 193 reported AEs (ISS, p.267).

Lundbeck reported that through the 120 Day safety Update, in the Phase II/III LGS trials, 93 subjects discontinued clobazam and no withdrawal-related AEs were reported (120 Day Safety Update, p.98).

In addition to the above analyses, in trials OV-1022, OV-1023, and OV-1038, investigators administered the Clinical Institute Withdrawal Assessment for Benzodiazepine (CIWA-B) questionnaire to study subjects. This instrument includes 20 questions and each response is given a numerical value from 0 (no withdrawal symptom) to 4 (most severe symptom) (Trial report, OV-1038, p.29). Using this instrument, there did not appear to be a clear relationship between withdrawal symptom risk and dose. Lundbeck reported that following abrupt discontinuation of 40 mg/day clobazam dosing, CIWA-B scores ranged from 0 to 56, indicating benzodiazepine withdrawal symptoms were nonexistent or mild for nearly all subjects. Following abrupt discontinuation of 120 mg/day dosing, CIWA-B scores ranged from 0 to 23, while following abrupt discontinuation of 160 mg/day dosing, CIWA-B scores ranged from 0 to 59.

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

Lundbeck reviewed the available post marketing safety data as part of the clobazam NDA. Sanofi-Aventis markets clobazam in over 80 countries and clobazam was first approved in Australia over 40 years ago (b) (4)

[Redacted]

Postmarketing exposure

[Redacted] (b) (4)
From 1998 until 2/28/10, the estimated exposure to clobazam was [Redacted] (b) (4) person years. The exposure estimates suggest that use has been increasing from [Redacted] (b) (4) person years (2/7/98-2/6/99) to [Redacted] (b) (4) person years (3/1/09-2/28/10).

Post marketing reports

Lundbeck summarized information from the post marketing reports for clobazam. After providing counts and demographic data, Lundbeck provided more in depth summaries

for reports with an outcome of death and for the reports of the same AEs of special interest examined in the clinical trials database (i.e., blood dyscrasias, pneumonia, severe or serious skin reactions, potential DILI, cancer, and DRESS syndrome).

Lundbeck reported that through 11/30/10, there were 2,043 post marketing reports that described 4,335 AEs in patients treated with clobazam (120 Day Safety Update, p.57). Lundbeck acknowledged that the report total may include duplicate reports (120 Day Safety Update, p.53). The post marketing reports were submitted spontaneously (n=1,868), were included in publications (n=155) and were from unidentifiable sources (n=20). The most commonly reported indication for clobazam use recorded in these reports was seizures (n=759). Other commonly reported treatment indications were therapeutic procedures and supportive care NEC (n=349), and anxiety disorders and symptoms (n=133) (120 Day Safety Update table 25, p.55).

Lundbeck summarized demographic data for the patients described in the post marketing AE reports. For the 1,415 reports with age data summarized in the ISS, the mean age was 34.7 years (median 33 years, range <1 day to 93 years). Through the 120 Day Safety update, the age distribution for the 1459 reports with age data was 80 reports for patients <2years old, 222 reports for patients aged 2 to <=12 years, 84 reports were for patients >=12 years and <16 years, 884 reports for patients ≥ 16 years to < 65 years, 109 reports for patients ≥ 65 to < 75, and 78 reports were for patients > 75 years. For the 1,791 reports that included patient sex, 56% (n=1010) were females and 44% (n=781) were male (120 Day Safety Update, p.57).

Lundbeck grouped AEs into MedDRA system organ classes (SOCs), and the most commonly reported AE SOCs were: Nervous system disorders (25.3%, n=1097), Psychiatric disorders (14.6%, n=632), General disorders and administrative site conditions (13.4%, n=582), Skin and subcutaneous tissue disorders (6.4%, n=278), Injury, poisoning, and procedural complications (5.7%, n=245), Investigations (5.7%, n=245), and Gastrointestinal disorders (5.5%, n=238)(120 Day Safety Update, p.58). Lundbeck also provided the SOCs groupings of AEs for the pediatric age group (<16 years). As with the overall group, Nervous system disorders (21%, n=193), General disorders and administrative site conditions (14%, n=123), and Psychiatric disorders (n=99, 11%) and were the most commonly reported AE SOCs for pediatric patients (120 Day Safety Update, p.61).

In their table 28 in the 120 Day Safety Update, Lundbeck listed the most commonly reported post marketing AEs (at least 1% of all AEs). I provide the information from that table below.

Most frequently reported post marketing AEs (>=1% of all AEs) for clobazam, through 11/30/2010

Preferred term	% (n)
Somnolence	5.1% (220)

Convulsion	3.2% (140)
Drug exposure during pregnancy	2.0% (88)
Drug ineffective	2.0% (87)
Drug interaction	1.7% (74)
Dizziness	1.7% (79)
Agitation	1.4% (60)
Headache	1.3% (57)
Insomnia	1.3% (57)
Aggression	1.2% (50)
Rash	1.1% (48)
Weight increased	1.1% (47)
Fatigue	1.1% (44)
Epilepsy	1.0% (43)
Asthenia	1.0% (42)
Tremor	1.0% (42)

From Table 28, 120 Day Safety Update, p.59.

In the pediatric group (<16 years old), the most frequently reported individual post marketing AEs were somnolence (5.0%), convulsion (3.2%), drug exposure during pregnancy (2.5%), drug interaction (2.1%), and aggression and drug ineffective (1.8%, each).

Post Market Reports with an Outcome of Death

For post marketing reports with a fatal outcome, Lundbeck used a data cutoff date of 3/11/11. Lundbeck reported that through 3/11/11 there were 74 post marketing reports with an outcome of death (69 through the ISS cutoff of 6/30/10, 3 through 12/1/10 and 2 through 3/11/11). In many of these cases, the reporter did not identify a specific cause of death. Lundbeck did group the cases by the circumstances surrounding the death. I summarize that information in the following table.

Causes/Circumstances of Death for Post Marketing Reports with Fatal Outcome

Cause of death/Circumstances	N
Overdose	11
Drug exposure during pregnancy	9
Insufficient information	7
Pneumonia	5
Liver failure	5
Multi organ failure	4
Cardiac condition	4
Cerebrovascular disease	3
Respiratory depression	3
Restless/anxious	3
Seizure	3
Suicide	3
Myocardial infarction	2

Sudden death	2
Cardiorespiratory depression	1
Choking on food	1
Drowning	1
Fever	1
Fever post vaccination	1
Gaucher's disease	1
Overdose/preexisting respiratory problems	1
Pancreatitis	1
Septic shock/agranulocytosis	1
SUDEP	1

Post Market Report Events of Interest

Pneumonia

Lundbeck searched their post marketing report database for the terms pneumonia and pneumonitis. Lundbeck identified 23 AE reports with these search terms. Many of the reports identified concomitant factors that put patients at increased risk for pneumonia AEs (seizure disorders, neurological deficits, swallowing problems, etc.). In 4 cases, after starting clobazam, patients experienced increased secretions and difficulty managing secretions and subsequently developed pneumonia. In another 4 cases, pneumonia occurred in patients that developed altered level of consciousness on clobazam.

Blood Dyscrasias

Using the search terms from the standardized MedDRA query (SMQ) for hematopoietic cytopenias, Lundbeck identified 66 cases that included 101 blood dyscrasia AE terms. Lundbeck felt that 12 cases had a reasonable temporal association to clobazam but felt the reports did not provide “strong evidence of a causal relationship” (ISS, p.201). For the remaining reports, Lundbeck identified confounding factors such as concomitant medications, comorbid disease, and improvement while continuing clobazam treatment, as factors suggesting that clobazam was not causally associated.

The most commonly reported AE term was thrombocytopenia (n=28). Another 9 reports included the term platelet decreased. The other most commonly reported terms were neutropenia (n=13), leucopenia (n=10), pancytopenia (n=9), anemia (n=7). No other blood dyscrasia term was reported at least 5 times. Other infrequent events of potential concern include agranulocytosis (n=4), bone marrow failure (n=3), and aplastic anemia (n=2). Below I review details from the reports for some of these events.

Thrombocytopenia and Platelet Count Decreased

Lundbeck identified 28 post marketing reports of thrombocytopenia and 9 reports of platelet count decreased in patients treated with clobazam. I read the MedWatch report forms for these events. Assessment of the role of clobazam in these cases is difficult

because the majority of patients were concomitantly treated with other medications that have been associated with the development of thrombocytopenia (carbamazepine, valproate, phenytoin, etc.) or had underlying diseases that are confounding factors (HIV, viral infections, etc.). In some cases the reports support that clobazam was not likely related to the event because patients' platelet counts increased after stopping another suspect drug and continuing clobazam. Some patients had evidence of low platelet counts prior to starting clobazam. In other cases, the reports lack sufficient details and/or lab test results to allow adequate assessment of the event.

Pancytopenia

Lundbeck identified 9 cases of pancytopenia and none strongly suggested a relationship to clobazam. One patient was diagnosed with ALL, 2 weeks after starting clobazam. Two cases included no cell count results and lack sufficient details to evaluate the events. In the remaining cases, patients were taking concomitant medications or had underlying diseases that made it difficult to assess the role of clobazam.

Aplastic Anemia

Lundbeck identified 2 reports of aplastic anemia. The first report included few details, but noted that the patient had an abnormal blood count result prior to starting clobazam. The second report noted that the diagnosis was temporally related to treatment with ethosuximide, a drug associated with aplastic anemia. I summarize those events below.

Report 1058922 A female (age not reported) with partial epilepsy was treated with levetiracetam from April 2005 to July 2005. The report noted that the patient had "a mild abnormal blood count prior to treatment with levetiracetam". The report did not provide the supporting abnormal lab test results. In July 2005 she was started on clobazam. Her only other concomitant medication was Microgynon (ethinylestradiol and levonorgestrel). In September 2005 she was diagnosed with aplastic anemia. She did not respond to treatment with antilymphocyte globulin.

Report 1060615 A 9 year old female with epilepsy started selenicarb (valproic acid) on 10/13/04, and started clobazam on 3/16/05. Ethosuximide was started on 7/30/08. On 11/30/08 she was diagnosed with aplastic anemia. Clobazam and ethosuximide were discontinued. No additional information was provided.

Agranulocytosis

Lundbeck identified 4 reports of agranulocytosis. The first case (1048188) involved a 74 year old female who had been treated with clobazam for "years" and developed agranulocytosis 7 weeks after starting mianserin, a drug associated with development of agranulocytosis. The second case (1057972) was of a 67 year old female who was treated with clobazam, calcium bromolactobionate, ciprofibrate, ethanolamine acetylleucinate, all for unspecified indications and dirithromycin for tonsillitis. Dirithromycin was switched to amoxicillin/clavulanate and 6 days later she was diagnosed with agranulocytosis (amoxicillin has been associated with development of agranulocytosis). All drugs were stopped. The patient responded to treatment with Neupogen. The third case (1060955) described a female (age not reported) with epilepsy treated with clobazam, valproic acid, and levetiracetam who developed

agranulocytosis and decreased platelet count. The outcome was not reported. The final case (1061654) was confounded by multiple medications and underlying medical condition. A 17 year old female who presented comatose with a fever that was subsequently diagnosed a Sjogren's syndrome. On presentation WBC was 6.89. She was treated with acyclovir and cefotaxime and she experienced "epileptic crisis". AEDs administered included levetiracetam, clobazam, fosphenytoin, phenobarbital. She was also treated with multiple antibiotics (vancomycin, piperacillin/tazobactam, amikacin), cyclophosphamide, corticosteroids, propofol, thiopental, and midazolam. She developed pancytopenia and was diagnosed with toxic-like agranulocytosis. She developed sepsis, multiple organ failure, and died.

Bone Marrow Failure

Lundbeck reported 3 cases of bone marrow failure. Report 1049726 described a 45 year old male with epilepsy, HIV, HCV, HBV, alcoholism and cirrhosis who was treated with valproate (18 months), abacavir/lamivudine/zidovudine (18 months) and clobazam (2 days) when he was noted to have a Hgb of 7.5g/dL and a neutrophil count of 900/mm³. Ten days later his Hgb was 5.3g/dL and neutrophil count was 300/mm³. He was admitted, abacavir/lamivudine/zidovudine was stopped, and 9 days later valproate and clobazam were stopped. Bone marrow biopsy showed global marrow hypoplasia without fibrosis. He was treated with RBC transfusions. Six weeks after onset, blood cell counts were normal. Abacavir/lamivudine/zidovudine were restarted. Report 1055045 described a 16 year old female who developed TEN, bone marrow depression, and septicemia in the month after starting treatment with fluvoxamine, clomipramine, clorazepate, liquid paraffin, and possibly clobazam (conflicting information whether patient actually took clobazam). Report 1058207 described a 6 year old female who started clobazam on 1/17/06 (added to zonisamide). On 1/24 she started oseltamivir, acetaminophen, carbocysteine, rokitamycin and bifidobacterium for influenza. On an unspecified date, all medications but clobazam were stopped. On 2/2, she was diagnosed with erythema multiforme and clobazam was stopped. Her hospital course was complicated by bone marrow depression. She recovered.

Serious Skin Reactions

Using the Serious Cutaneous Adverse reactions SMQ, Lundbeck identified 24 reports of serious skin reaction in patients treated with clobazam. Lundbeck identified 3 additional cases in the 120 day Safety Update. Lundbeck felt that 16 cases had either insufficient information to evaluate the events or the patients were taking multiple medications making it difficult to assess the role of clobazam. Lundbeck considered 3 cases (drug induced eruption, exanthematous pustulosis, and erythema multiforme exudativum) possibly related to clobazam. I provide details for those cases below.

DKLU1050631 describes a patient who experienced erythema while he was treated with carbamazepine and sodium valproate, which was diagnosed as drug-induced eruption. The medications were discontinued, and clobazam was initiated, although the eruption had not yet completely resolved. In (b) (6), approximately 1.5 months after drug was started, the eruption was aggravated, and fever and malaise appeared, becoming erythroderma-like the following month, with which the patient could not

move due to erythroderma and skin pain. The patient was hospitalized and treated with methylprednisolone and oral prednisolone. Clobazam was discontinued, and the patient was discharged 1 month later.

DKLU1059476 describes a patient on phenobarbital and lamotrigine who started clobazam, cephalexin, metronidazole, and methicillin. Skin lesions appeared 16 days later. Pyostacine and fluconazole were added, but the condition worsened. A skin biopsy revealed generalized exanthematous pustulosis or pustulosis psoriasis. At that time, pyostacine and clobazam were discontinued, and the condition improved.

DKLU1058207 describes a patient who was taking zonisamide for epilepsy and started clobazam. Two weeks following clobazam initiation the patient developed erythema multiforme exudativum. Clobazam was discontinued, and the event resolved. Zonisamide was continued.

Lundbeck felt 3 reports identified reasonable alternative explanations for the event. One patient with a history of SJS with carbamazepine experienced SJS when carbamazepine was restarted. In a second case, a patient taking clobazam carbamazepine, clonazepam, and valproate for 1 year and lamotrigine for 20 days developed TEN. Drug lymphocyte stimulation test was positive for valproate, lamotrigine, and negative for carbamazepine, clobazam, and clonazepam. The third case was a patient who developed DRESS, which was attributed to treatment with strontium.

Lundbeck found that the remaining 5 cases documented either resolution with continued clobazam treatment, negative rechallenge, or temporal implausibility (event occurred after 10 days of oxcarbazepine, had been taking clobazam for years) (ISS, p.202).

In the following paragraphs, I provide additional information for the post marketing reports of SJS (n=4), and TEN (n=7).

SJS

Lundbeck identified 4 post marketing reports of SJS. Report 1047915 was initially reported as SJS but subsequently published as a case of photo-induced TEN (appears as report 1048331). The 23 year old female patient had been treated with clobazam for 2 weeks (for alopecia areata), and developed vesicular eruptions, initially on light exposed areas, then spreading to all areas, and with mucosal involvement. The patient was hospitalized for 3 weeks and recovered. The second case (1059325) was a 4 year old male treated with valproic acid for 3 years, lamotrigine for 1 month and clobazam for 10 days who developed oral mucosal ulcerations, hyperemic conjunctiva, ulcerations on the genital region and purpuric lesions on the trunk. Lamotrigine was stopped (clobazam continued) and the patient was treated with steroids and the lesions resolved. The third case of SJS (1060730) described a 16 year old female treated with carbamazepine. Phenytoin was added but stopped after 1 week for fevers and rash. The next day, clobazam was added. A week later, the patient's condition progressed to include erosions and blisters on her legs, fingers, oral mucosa and conjunctiva. Clobazam and carbamazepine were stopped. Clobazam was re-started 1 month later

without recurrence of SJS. The final case (1060908) described a 44 year old male with a history of SJS on carbamazepine experienced SJS while being treated with carbamazepine and clobazam.

TEN

As explained above, the first case (1048331) was initially reported as SJS but subsequently published as a case of photo-induced TEN. The second case (1050077) occurred in a 30 year old female treated with clobazam and moclobemide and no other details were provided. The third report (1055045) was of a 16 year old female who developed TEN within 8 days of starting fluvoxamine, and while treated with clorazepate, and shortly after stopping clomipramine. The narrative could not confirm that the patient was taking clobazam (could not establish if a prior prescription was filled). She developed skin lesions over 60% of her body and had mucosal lesions. She also experienced bone marrow depression (described above). The fourth case (1055687) only reported that a 35 year old female taking clobazam and loprozalam experienced Lyell syndrome (TEN) and recovered. The fifth case (1059351) was a 58 year old male who had been treated with clobazam (for over 1 year), carbamazepine, valproate, clonazepam (duration unknown) and lamictal (20 days) developed TEN. Lamotrigine and clobazam were stopped. The sixth case of TEN (1059703) was a 62 year old female who underwent surgery for a meningioma. Fifteen days post op, while treated with clobazam, carbamazepine, zolpidem, fluoxetine, paracetamol/dextropropoxyphene, and calcium nadroparine, she developed TEN. No other details were provided. The last case (1064308), identified in the 120 day Safety Update, was a 15 year old female who developed TEN (fever, stomatitis, cutaneous and mucosal ulcerations, conjunctivitis) 15 days after starting clobazam, oxcarbazepine, and olanzapine. All 3 drugs were stopped and the patient improved.

Drug Induced Liver Injury

Using the DILI SMQ, Lundbeck identified 54 cases of potential liver injury. Lundbeck identified 4 additional liver injury reports in the 120 day Safety Update. Of all the reported cases, Lundbeck felt that only one case was possibly related to clobazam. I provide details for that event below.

DKLU1060307 reports events that occurred following a 24-day exposure to clobazam in a patient who, although reporting multiple concomitant medications including AEDs, had no other medication changes. AST and ALT increased to 132/133 IU/L after 2 weeks of clobazam administration and to 233/248 IU/L after 1 month, respectively. However, they recovered to normal levels after the discontinuation of the drug. Bilirubin was not reported. Events resolved following drug discontinuation, and the patient recovered.

Lundbeck felt three cases included alternative plausible explanations for liver injury (CMV infection, abnormal LFTs prior to starting clobazam, and use of Chinese herbs). Six events improved or resolved with continued clobazam. For the remaining cases, Lundbeck was unable to assess causality due to the use of multiple medications (n=36) or the lack of clinical details (n=13).

From the list of MedWatch reports, I selected a subset that represented potentially concerning liver injuries and read those reports to look for evidence of a causal relationship to clobazam. None of the reports clearly suggested that clobazam was causally related to the event. None of the reports described a positive rechallenge with clobazam. In none of the reports was clobazam the only medication being taken at the time of the event. In many of the reports, the patients were taking other medications that have been associated with hepatotoxicity. In some cases, patients were treated for years with clobazam prior to the onset of liver injury event. Some cases documented resolution of the event with continued clobazam treatment and some documented negative clobazam rechallenges. Some cases included too few details to adequately evaluate the adverse event. I summarize information from select hepatic injury reports below.

Hepatitis

Lundbeck submitted 7 post marketing reports of hepatitis in patients treated with clobazam.

Report 1064197 described a 58 year old female with a history of cirrhosis and chronic hepatitis who died and the reported cause of death was acute hepatitis. Her medications were flupentixol decanoate IM, topiramate (since 2001), meprobamate (since 2003), paracetamol (since 05 June 2010), tropatepine (since 15 June 2010) and clobazam (from 03 to 18 June 2010). On [REDACTED] (b) (6) the patient was admitted for seizures. Laboratory tests showed SGPT 1945 IU/L, SGOT 2399 IU/L, alkaline phosphatase 154 IU/L, total bilirubin 237 µmol/L and direct bilirubin of 233.6 µmol/L. Previous laboratory data on 30 April 2010 were unremarkable. Flupentixol had been discontinued on 07 June 2010. Levetiracetam and paracetamol were discontinued on 01 July 2010, and meprobamate on 02 July 2010. Abdominal ultrasound showed an absence of dilatation of the intrahepatic or principal biliary tracts. Serology for Virus B hepatitis: negative HBs-Ag but total antibodies anti-HBc positive at 651 (N: less than 500 U/mL), viral DNA HBV negative, HAV, HCV, HEV, HSV, CMV negative. Additional serologies: Negative for Chlamydia, Mycoplasma, Rickettsia and Syphilis, Negative for antibodies: antinuclear, anti-smooth muscle, anti-mitochondrion, antireticulum endoplasmic, anti-DNA. On [REDACTED] (b) (6) morning, the patient presented with blackish vomiting. Suspicion of mesenteric ischemia with occlusive syndrome was ruled out by abdominal CT scan. On [REDACTED] (b) (6) icterus was persisting; SGOT and SGPT were decreasing respectively to 485 IU/L and 373 IU/L, while bilirubin remained increased (direct bilirubin was 461 µmol and total bilirubin 536 µmol/L). Prothombin ratio and coagulation factor II were decreased to 47% and 34%, respectively. On [REDACTED] (b) (6), at [REDACTED] (b) (6) the patient died. On [REDACTED] (b) (6), post-mortem hepatic puncture was performed which diagnosed acute hepatitis with bridging necrosis especially of peri- and supra-hepatic areas. The final diagnosis was acute hepatitis. Frisium (clobazam) had

been administered from 03 to 18 June 2010 and the outcome for the event of acute hepatitis was fatal with date of death [REDACTED] (b) (6)

Report 1050147 described a patient who had been treated with carbamazepine, thioridazole, fluphenazine, and clobazam for 18 years and developed hepatitis after 3 days of ingesting paracetamol (estimate 3g/day) for headache. Report 1048561 described a patient who developed hepatitis on Tegretol and Dilantin, stopped those medications, started clobazam, and had progression of hepatitis. He stopped clobazam, recovered, and later restarted clobazam without recurrence of hepatitis. Report 1055096 noted that a 19 year old female treated with valproic acid and clobazam developed hepatitis, encephalopathy, pancreatitis, and died. No other details were included in the report. Report 1060557 described a 19 year old male who was treated with cyamemazine and clobazam for 8 days, stopped both, took 1 additional dose of clobazam 15 days later and the next day began experiencing malaise, chills and asthenia. The following day he took oxazepam and developed dark urine, fever, and abdominal pain. He was treated with ibuprofen, prazepam, and paracetamol. Five days later, he had elevated transaminases (4-5 times ULN), elevated bilirubin and eosinophilia. Serology was negative for Hepatitis A,B, and C, toxoplasmosis, EBV, HIV, CMV, and HSV. ANA was >1280 and anti smooth muscle antibody was 80. Ultrasound documented dilated intrahepatic biliary ducts. Report 1059213 described a 72 year old male who was started on clobazam and levetiracetam, and the next was also given phenytoin and topiramate. Five days later, he developed increased transaminases and alkaline phosphatase. No other details were provided. Report 1047542 described an 8 year old male who developed elevated transaminases and decreased prothrombin (with normal bilirubin and alkaline phosphatase) while treated with clobazam, valproic acid, and trileptal.

Hepatitis Fulminant

Report 1061829 described a 37 year old male patient who had been taking clobazam, phenobarbital, and valproic acid for 10 years who developed liver injury (elevated transaminases, coagulopathy) 7 months after starting allopurinol and Chinese herbal preparations.

Hepatic failure

Lundbeck provided 4 reports of hepatic failure (hepatic failure n=3, acute hepatic failure n=1). Report 1048455 described a 21 year old female who developed hepatic failure (no lab results) 3 months after starting valproic acid, phenytoin, clobazam, metoclopramide, and chloral hydrate. Report 1055096 described a 19 year old female treated with clobazam and valproic acid who developed encephalopathy, pancreatitis, anuria, shock, liver failure, and death (no lab results or description of diagnostic evaluation). Report 1058591 described a 20 year old female treated with clobazam, valproic acid, and ethinyl estradiol who developed increased transaminases (4-5x ULN) with normal PT, ALP, GGT, and bilirubin. Valproic acid and clobazam were stopped. She was treated with cefpodoxime and paracetamol for dry cough and flu symptoms. Repeat

transaminases showed increases to >70x ULN and elevated bilirubin. She was treated with N-acetylcysteine. Liver biopsy showed microvesicular steatosis with septal fibrosis and perisinusoidal necrosis, felt compatible with valproic acid induced hepatitis. She underwent a liver transplant, experienced status epilepticus and died. Report 1060738 described a 7 month old male treated with clobazam, valproic acid, topiramate, stiripentol, and clonazepam who developed post febrile status and was diagnosed with hepatic, renal, and neurological failure.

Jaundice

Lundbeck submitted 4 post marketing reports of jaundice. Based on the documentation of the same reporting country, demographics, concomitant medications, and test results, two reports appear to be describing the same event. Therefore, there appear to be 3 unique post marketing reports of jaundice. Reports 1050330 and 1055483 describe a 33 year old male treated with minaprine, amineptine, and clobazam and developed icterus and had a liver biopsy demonstrating cholestatic hepatitis. Amineptine, a tricyclic antidepressant, has been associated with the development of cholestatic and mixed hepatitis. Report 1057976 described a 74 year old female treated with clobazam, zolpidem, trimetazidine, ginkgo, folic acid, paroxetine, amoxicillin/clavulanate, an amikacin who developed icterus and pruritis. All drugs were stopped and she improved. The report noted that tests for Hepatitis A,B, and C were negative. Report 1060557 was also coded as a hepatitis event and is summarized above with those reports.

Hepatotoxicity

Report 1060541 described a 5 year old female treated with stiripentol, clobazam, and valproic acid, who developed hepatic toxicity that was not described further.

Cytolytic Hepatitis

Report 1051550 described a 19 year old male who previously experienced hepatitis while treated with carbamazepine. He was treated with clobazam, topiramate, and levetiracetam for 2 years and was hospitalized for frequent seizures with “pharyngeal blocking”. He had an experienced a BP of 10mmHg and a HR of 130. He was treated with antibiotics and subsequently developed hepatic cytolysis. The narrative provided no additional details about the event.

Liver Injury

Lundbeck summarized 5 post marketing reports that were coded as liver injury. Report 1069924 described a 12 year old female with seizure disorder and developmental delay who was treated with carbamazepine, haloperidol, chlorpromazine, clobazam, imipramine, and Phenobarbital. She was hospitalized for seizures and had an SGOT of 71 U/L, and SGPT of 27 U/L, and a GGT of 95 U/L. Five months later, SGOT was 610U/L, SGPT was 346 U/L, and total bilirubin was 9.7mg/dL. Serology was negative for hepatitis A, B, and C, anti-HIV, cytomegalovirus, toxoplasmosis, and Epstein-Barr virus. Her hospital course was notable for extreme aggression, confusion, pneumonia, pulmonary hemorrhage, respiratory arrest, and death. Post mortem liver examination

showed global retraction and clear segmental involvement of right greater than left lobe, which was described as greenish, 'bosselated', nodular, and irregular. On the right, there was predominance of fibrosing and massy pattern. Microscopic findings included torsion of architecture, with formation of irregular nodules and biliary intra and extracellular pigments, and variable peri-portal and peri-septal inflammatory process. Report 1049122 described a 4 year old male treated with valproic acid, ethosuxamide and clobazam who developed pancreatitis, decreased cholinesterase, coagulation disturbances and liver injury (not described). The 3 remaining reports (1046003, 1046006, and 1046500) included few details but mentioned increases in transaminases.

Cancer

Lundbeck identified 11 post marketing reports of patients diagnosed with malignancies. Lundbeck felt that for most cases either the exposure was temporally implausible, the reports did not provide adequate information, or the report identified an adequate alternative etiology (hepatic adenoma in a patient taking oral contraceptives). Lundbeck noted for one other case, a 14 year old diagnosed with leukemia, that the patient had been treated with multiple medications which precluded causal assessment for any single drug.

I read the reports that Lundbeck identified as malignancies. One report (1060854) described a patient who developed "itchy red lumps" that were not diagnosed as a malignancy. The remaining diagnoses were glioblastoma recurrence, promyelocytic leukemia, acute lymphocytic leukemia, acute leukemia (not further specified), astrocytoma, mycosis fungoides (n=2), myelodysplastic syndrome, hepatic adenoma, and non Hodgkin's lymphoma.

SUDEP

Lundbeck identified one post marketing report that was coded as SUDEP. They did not appear to assess all reports of sudden deaths in attempt to identify potential cases of SUDEP. The SUDEP case that Lundbeck identified was reported in the medical literature. The patient was a 14 year old male treated with carbamazepine and clobazam who was found dead at home the day after experiencing 2 or 3 seizures.

DRESS

To identify post marketing cases of potential DRESS, Lundbeck searched their database for the following AE terms: fever/pyrexia or rash or lymphadenopathy. This search identified 98 unique reports. Lundbeck then manually reviewed the reports to identify cases that included internal organ or hematologic involvement. From this evaluation, Lundbeck identified 7 potential reports of DRESS.

In all 7 cases, the patients were treated with multiple medications, complicating any causal assessment. One report noted a negative rechallenge with clobazam, other reports noted resolution with continued clobazam treatment and one report identified an

alternative etiology for the event (strontium). I provide summaries for these cases below.

DKLU1003809/DKLU1050658 reports events of rash, eosinophilia, and fever in a 46-year-old patient treated with citalopram and clobazam for approximately 6 weeks when hospitalized for febrile exanthem associated with cheilitis, lymphadenopathy and disturbance of vigilance. WBC increased to 60,200 with 30% eosinophils and abnormal hepatic enzymes (NOS). Cutaneous biopsy showed a layer of C1q on vascular structures and an infiltration of immunoglobulin on direct fluorescent antibody test. Follow-up patch tests with citalopram were positive.

DKLU1048035 reports pancytopenia, maculopapular rash, and serum glutamic oxaloacetic transaminase (SGOT)/serum pyruvic transaminase (SGPT) increased in a patient with a history of hyperimmunoglobulinemia D (hyper IgD syndrome) treated with clobazam, sulfamethizole / trimethoprim (Bactrim), and domperidone. Symptoms occurred 12 days and 9 days after the patient was started on clobazam and Bactrim, respectively. Lab tests were at a maximum / minimum of 1.8 WBC, 8 ULN SGOT, 2.5 ULN SGPT, and 31 platelets. The event resolved, and the reporter determined the final diagnosis to be macrophage activation syndrome of unknown etiology.

DKLU1048561 reports hepatitis, generalized macular rash, coagulopathy, and hepatomegaly in a 13-year-old male patient who started clobazam for convulsions on [REDACTED] (b) (6), following his last dose, he developed a generalized macular eruption, hepatomegaly, and coagulopathy and was hospitalized. Fourteen days prior to this event, a similar reaction had occurred with Tegretol and Dilantin. During hospitalization, liver biopsy revealed that the patient was suffering from acute hepatitis with necrosis compatible with a toxic reaction. Clobazam was discontinued, and lab values were prothrombin time of 18.4/10.5, AST 6614; ALT 6047; GGT 576; total bilirubin 36 and direct bilirubin 24 (units not provided). Clobazam was subsequently restarted 26 June 1994 with no recurrence of symptoms.

DKLU1050554 reports erythematous rash, fever, thrombocytopenia and hepatic function abnormal. The patient was a 16-year-old female with a medical history of epilepsy and recurrent urticaria eruptions who was treated with clobazam (Urbanyl) and carbamazepine for 4 weeks. An erythematous rash on the face, fever, thrombocytopenia and hepatic cytolysis (NOS) were reported, and carbamazepine was stopped. The patient progressed to oedema of face, eyelids and lips with a fever of 39° Celsius. The patient was hospitalized for papulous erythrodermia, and an erythematous pustular pharyngitis developed. The cutaneous lesions improved with hydroxyzine, cetirizine and prednisone. Hypersensitivity to carbamazepine was diagnosed. Cutaneous biopsy was more in favor of lupus than of toxidermia, but no antibodies were found. Action with clobazam was not reported.

DKLU1057941 reports DRESS syndrome, dermatitis exfoliative and mucous membrane disorder. This 70-year-old female patient began treatment with clobazam in April 2007 for an unknown indication. In 14 June 2007, the patient began taking an unknown dose of Strontium ranelate for an unknown indication. Additional medications added between these months included calcium carbonate cholecalciferol, trospium chloride, piribedil, phloroglucinol/simethicone, domperidone, and silettum. Longstanding medications include fluoxetine and levothyroxine for 20 years. [REDACTED] (b) (6), the patient experienced DRESS syndrome with erythroderma, mucosa lesions, and hepatic diseases leading to her hospitalization. All of the patient's concomitant medications were discontinued with the exception of levothyroxine. The patient was treated and recovered. It was reported that the DRESS syndrome experienced by the patient was due to strontium ranelate.

DKLU1057979 reports fever, maculopapular rash, hepatomegalia and cholelithiasis. This was a 65-year-old male patient with a medical history of epilepsy and alcoholic liver cirrhosis. The patient was hospitalized on [REDACTED] (b) (6) for epilepsy. He was treated with clobazam (dosage unspecified), and phenobarbital was introduced. Two days later he experienced a maculo-papular rash that became

generalized after treatment with cortisone. Certirizine and phenobarbital were discontinued, intravenous dexchlorpheniramine and topical corticosteroid were administered, and the patient fully recovered.

DKLU1061804 is a literature report of acute interstitial nephritis coincident with clobazam, phenytoin and lamotrigine in a 47-year-old patient who had taken multiple antiepileptic drugs over 10 years. Acute symptoms were nausea, vomiting, pain, oliguria with elevated liver function tests (AST 152 IU/L; ALT 1774 IU/L, gamma glutamyl transferase 415 IU/L). Creatinine was 16.7 mg/dL, and a renal biopsy was performed. A diagnosis of acute allergic interstitial nephritis was made, and the patient was treated with steroids and hemodialysis and recovered.

9 Appendices

9.1 Literature Review/References

Referenced articles are reviewed above.

9.2 Labeling Recommendations

(b) (4)

The Warnings and Precautions statements should be re-ordered as follows:

- 5.1 (b) (4)
- 5.2 Concomitant Use with Central Nervous System Depressants
- 5.3 Withdrawal
- 5.4 Physical and Psychological Dependence
- 5.5 Suicidal Behavior and Ideation

The Warnings and Precautions statement about withdrawal (5.3) should be reworded to read as follows:

5.3 Withdrawal

[Redacted] (b) (4)

As with all antiepileptic drugs, ONFI should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.

Withdrawal symptoms, (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time followed by an abrupt discontinuation. Generally milder withdrawal symptoms (e.g., dysphoria, anxiety, and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic doses for several months.

Withdrawal symptoms occurred following abrupt discontinuation of ONFI (b) (4)

[Redacted] (b) (4)
[Redacted] (b) (4)
[Redacted] (b) (4)
[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

In section 7, Drug Interactions, Lundbeck should include the following language:

Strong inhibitors of CYP2C19 may result in increased exposure to N-CLB, the active metabolite of clobazam. Dosage adjustment of ONFI may be necessary when coadministered with strong CYP2C19 inhibitors (e.g. fluconazole, fluvoxamine, ticlopidine) [Redacted] (b) (4).

9.3 Advisory Committee Meeting

The Division did not present the clobazam NDA to an Advisory Committee.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GERARD A BOEHM
08/24/2011

SALLY U YASUDA
08/24/2011