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RESEARCH**

APPLICATION NUMBER:

206030Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

PRODUCT (Generic Name):	Carbamazepine
NDA:	206030 (0000)
PRODUCT (Brand Name):	Carbella™
DOSAGE FORM:	Solution for IV Infusion
INDICATION:	Replacement therapy in adults (18 years and older) with the following seizure types when oral carbamazepine administration is temporarily not feasible: partial seizures with complex symptomatology, generalized tonic-clonic seizures, mixed seizure patterns which include the above, or other partial or generalized seizures
NDA TYPE:	505(b)(2)
SPONSOR:	Lundbeck
IND :	073686
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1. EXECUTIVE SUMMARY

Carbella is a solution containing carbamazepine (CBZ) for intravascular (IV) infusion. The sponsor pursued a 505(b)(2) pathway using Carbatrol®, Tegretol®, and Tegretol® XR as reference listed drugs (RLDs). CBZ oral tablets have been previously approved for various indications including use as an anticonvulsant. Sponsor is seeking an indication of replacement therapy in adults (18 years and older) with the following seizure types when oral carbamazepine administration is temporarily not feasible: partial seizures with complex symptomatology, generalized tonic-clonic seizures, mixed seizure patterns which include the above, or other partial or generalized seizures. Sponsor proposed to administer 70% of the daily oral dose administered as a (b) (4) 30-minute IV infusion every 6 hours during each day of IV infusion.

In this submission, Sponsor conducted a comparative PK study (OV-1015) as well as a safety study (13181A where PK data were not collected) to support approval. Study OV-1015 compared steady state oral CBZ pharmacokinetics in epilepsy patients with the pharmacokinetics of an intravascular infusion of 70% of the total 24-hour oral dose administered every 6 hours. In addition, Sponsor characterized the PK of Captisol (the Carbella solubilizing agent) in study OV-1015. OV-1015 enrolled patients that were receiving oral CBZ every 6, 8, and 12 hours. In order to design the dosing regimen for study OV-1015, Sponsor acquired data from another Sponsor (The University of Minnesota) that was acquired from the bioavailability study 15926A (funded by NINDS) which administered oral CBZ as well as an IV CBZ formulation. Sponsor conducted a PK analysis of the NINDS PK data and estimated absolute bioavailability of oral CBZ. The bioavailability estimate was used for dose selection in study OV-1015. In addition, the Sponsor conducted PK simulations based on OV-1015 PK data to determine if adjusting dose and dose regimen parameters may produce IV CBZ concentration profiles that may be more comparable to oral CBZ profiles than was observed in study OV-1015. In addition, partial AUC (pAUC) values as well concentrations at individual time points were compared with those of RLD. No efficacy trial was conducted for Carbella.

The IV CBZ concentration profile at steady state (after 7 days of IV administrations) was lower than the steady state oral CBZ concentration profile. However, the difference between the IV and oral CBZ concentrations (e.g. concentration 6 hours after an oral administration at steady state minus the concentration 6 hours after an IV infusion on Day 7) is comparable to intrasubject oral PK variability (in terms of C_{min} values measured on Days -14, -1, and 0). As such, from a clinical pharmacology perspective, the magnitude of the decrease of IV steady state CBZ concentrations compared to oral steady state concentrations is not expected to result in a worsening of efficacy.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 1 (DCP-1) has reviewed the NDA (b) (4) and found the application is acceptable from a clinical pharmacology standpoint.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

CBZ PK data was obtained from Study OV-1015, a pivotal PK study which compared CBZ exposure from steady-state oral therapy with CBZ exposure after 1 day and after 7 days of q6h IV CBZ administration in epilepsy patients. The results of study OV-1015 demonstrated comparable BA between oral and IV C_{min} , C_{max} , and AUC_{0-24} for the 30-minute infusion, 70% oral-to-IV daily dose conversion, when infused Q6h.

Despite the comparable C_{min} , C_{max} , and AUC_{0-24} , comparison of the steady state oral PK with IV PK revealed that mean CBZ concentrations were lower from about 1 to 6 hours post infusion. Within each subject, the mean decrease in concentration between the IV C_{6h} (6 hours after IV infusion onset) and the patient's oral C_{6h} (6 hours after oral administration) was 2 µg/mL. However, patients in this study demonstrated that over a 2-week period, the intrasubject C_{min} fluctuation is, on average, 1.7 µg/mL. In light of the magnitude of observed intrasubject C_{min} variability during steady state oral CBZ therapy, the 2 µg/mL decrease due to IV CBZ administration is not expected to result in a worsening of efficacy. PK simulations demonstrate that when switching from oral Q6h to IV Q6h, the steady-state IV C_{6h} values are, on average, 1.4 µg/mL lower than steady-state oral C_{6h} on an intrasubject basis. This IV C_{6h} decrease when switching from oral q6h CBZ is consistent with the C_{6h} decrease observed in patients switching from oral q8h and oral q12h. As such, the PK simulations are supportive of Carbella use with patients receiving oral q6h CBZ.

Though the Sponsor recommended (b) (4) 30-minute infusion, the 30-minute infusion duration is recommended as it is associated with fewer adverse events, lower C_{max} values, (b) (4).

Overall, the 30-minute infusion, q6h, at a 70% oral-to-IV conversion is the recommended dose regimen. Due to observed kidney damage that is likely due to the solubilizing agent, Captisol, the recommended monitoring assessments for patients receiving Carbella include a complete urinalysis, creatinine, and blood urea nitrogen (BUN). Carbella is not recommended for use in patients with moderate or severe renal impairment or ESRD.

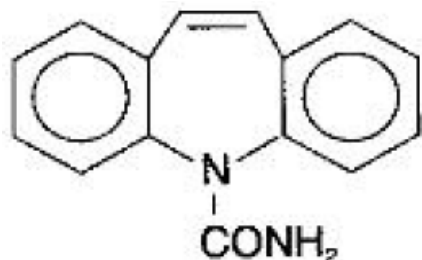
2. QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1. Drug/Drug Product Information

CBZ is chemically unrelated to other anticonvulsants. The mechanism of action is unknown, but CBZ appears to act by reducing polysynaptic responses and blocking post-tetanic potentiation. The molecular weight is 236.27.

Figure 1: Chemical Structure of Carbamazepine



2.1.2. Formulation

Carbella comes in a vial containing 200 mg CBZ in 20 mL of fluid (10 mg/mL Carbamazepine). The formulation contains 250 mg/mL Captisol. The Carbella solution is mixed with 100 mL of diluent solution (b) (4) to create the solution for infusion. The following table describes the preparation and administration of Carbella for Infusion.

Table 1: Preparation and Administration of Carbella for Infusion

Total Daily Oral CBZ* Dose (mg/day)	70% Adjusted Total Daily Dose (mg/day)	CARBELLA Single Dose (mg/q6h)	CARBELLA Single Dose Volume (Vials Required)	Diluent Volume	Infusion Duration	Dose Frequency within 24 Hours
400	280	70	7 mL (1)	100 mL	30 min	Every 6 hrs
600	420	105	10.5 mL (1)			
800	560	140	14 mL (1)			
1000	700	175	17.5 mL (1)			
1200	840	210	21 mL (2)			
1400	980	245	24.5 mL (2)			
1600	1120	280	28 mL (2)			

2.1.3. Mechanism of Action

The mechanism of action remains unknown. CBZ appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation.

2.1.4. Indication

CARBELLA injection is an antiepileptic drug indicated as replacement therapy in adults (18 years and older) with the following seizure types when oral CBZ administration is temporarily not feasible:

- Partial seizures with complex symptomatology
- Generalized tonic-clonic seizures

- Mixed seizure patterns which include the above, or other partial or generalized seizures

2.1.5. Proposed dose and dosing regimen

The total daily dose of Carbella is 70% of the established total oral daily dose, given in 4 divided doses administered every 6 hours. Each dose of Carbella should be diluted in 100 mL of a compatible diluent and intravenously infused over a period of (b) (4) 30 minutes. At the end of the intravenous replacement period, patients switch back to oral CBZ administration at their prior daily dose and frequency.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1. What are the design features of the clinical pharmacology and efficacy studies used to support dosing or claims?

In this submission, no efficacy studies were conducted. A relative bioavailability study for CBZ, analysis of Captisol PK from the relative BA study, and PK analysis study using data provided by a NINDS study were conducted by the sponsor to support the approval of Carbella:

Table 2: Summary of Clinical Studies Where PK Data Were Collected or Analyzed

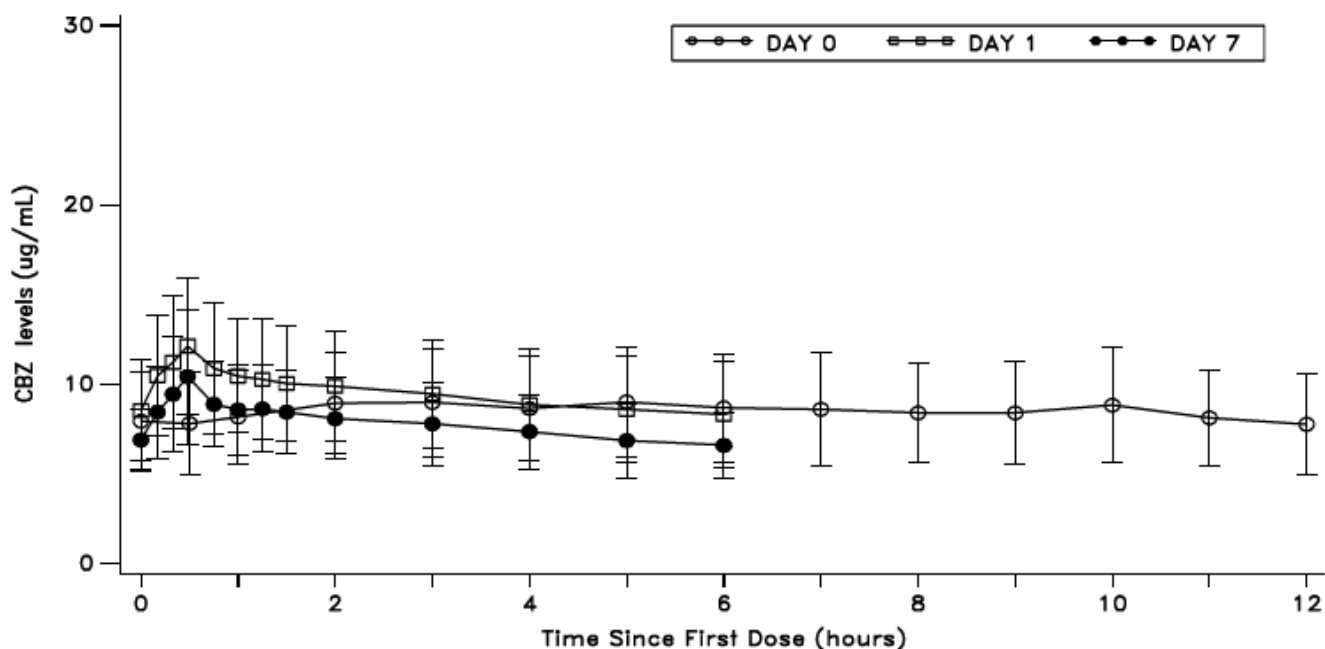
Type of Study and Study Identifier	Objective(s) of the Study	Study Design	Doses, Route, Regimen	n	Healthy or Patients
OV-1015 Relative BA	To assess safety, tolerability, and PK of IV CBZ as a 30- and 15-minute infusion relative to orally administered CBZ in patients with epilepsy.	Open-label, sequential	IV infusion of 70% of total oral daily dose, administered q6h	98	Epilepsy patients
15875a Captisol PK Report (Study OV-1015)	Assess: • Single and multiple dose Captisol PK • Mild RI effect on Captisol • Effect of infusion duration on Captisol PK	Open-label, sequential	25 mg Captisol per 1 mg CBZ administered in study OV-1015	53	Epilepsy patients
15841a Supplemental Captisol PK Report (Study OV-1015)	Assess the effects of infusion duration on Captisol PK within patients with normal renal function as well as mild RI	Open-label, sequential	25 mg Captisol per 1 mg CBZ administered in study OV-1015	53	Epilepsy patients
15926a Pop PK Analysis of Data from a	Estimate CBZ bioavailability Assess Single-dose IV CBZ PK	Open-label	100 mg stable-labelled CBZ (dissolved in Cavitron®) infused	76	Epilepsy patients

NINDS-Sponsored Study Conducted at The University of Minnesota	Predict Steady-State CBZ concentrations Determine optimal infusion duration		intravenously plus an oral CBZ dose that is 100 mg less than normal oral CBZ dose		
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2.2.2. What are the PK characteristics of the drug?

The following figure illustrates the mean PK profile for all subjects with normal renal function that participated in study OV-1015.

Figure 2: CBZ PK Profile (Mean $\pm$ SD) During Oral Administration (Day 0), On the first Day of IV Administration (Day 1), and Last Day of IV Administration (Day 7) for a 70% Oral-to-IV Conversion, 30-Minute Infusions, Administered Q6h During Study OV-1015



(source: ov-1015-study-report-body.pdf, page 77/6880)

Additional pharmacokinetic parameters are summarized in the following table.

Table 3: Steady-State Plasma CBZ PK Parameters Following Oral and IV Administration in study OV-1015

Parameter Variable	Normal Renal Function ¹			Mild Renal Impairment ¹	
	2-5-minute Infusions ²	15-minute Infusions ²	30-minute Infusions ²	15-minute Infusions ²	30-minute Infusions ²
AUC(0-24) (µg·hr/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	189.85 (61.96)	191.45 (49.78)	204.58 (67.89)	193.41 (28.12)	177.02 (42.97)
%CV	32.64	26.00	33.19	14.54	24.27
Geometric mean	179.68	184.48	192.74	191.96	172.02
Median	195.99	193.72	207.76	185.85	189.07
Range	91.2 - 257.9	86.4 - 295.6	96.3 - 319.9	169.3 - 232.6	110.9 - 227.3
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	179.42 (50.85)	180.08 (45.05)	186.40 (52.27)	184.61 (24.87)	152.99 (34.33)
%CV	28.34	25.02	28.04	13.47	22.44
Geometric mean	172.60	174.25	178.99	183.41	149.18
Median	182.09	167.59	185.20	178.24	153.45
Range	105.3 - 248.2	81.1 - 279.6	88.2 - 273.6	162.7 - 219.3	98.8 - 190.6
C_{max} (µg/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	8.97 (2.82)	9.05 (2.25)	9.81 (3.31)	9.35 (1.33)	8.49 (1.97)
%CV	31.47	24.85	33.74	14.19	23.26
Geometric mean	8.52	8.75	9.24	9.28	8.29
Median	9.35	9.05	9.82	8.93	8.38
Range	4.28 - 12.00	4.28 - 13.00	4.46 - 16.80	8.33 - 11.20	6.13 - 11.90
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	13.44 (6.85)	11.77 (4.05)	10.76 (3.76)	10.50 (2.40)	8.92 (1.93)
%CV	50.98	34.42	34.91	22.85	21.63
Geometric mean	12.09	11.14	10.15	10.29	8.74
Median	11.30	11.10	10.40	10.51	8.49
Range	4.72 - 27.50	4.79 - 23.80	4.53 - 20.20	8.09 - 12.90	6.47 - 12.00
C_{min} (µg/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	6.57 (2.28)	6.71 (1.91)	7.21 (2.47)	6.70 (1.02)	6.28 (1.76)
%CV	34.62	28.38	34.26	15.26	28.07
Geometric mean	6.19	6.43	6.77	6.64	6.05
Median	6.65	6.77	7.47	6.35	6.88
Range	3.06 - 9.89	2.90 - 11.60	3.16 - 11.90	5.89 - 8.19	3.65 - 8.52
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	6.18 (2.05)	6.01 (1.60)	6.28 (1.70)	5.81 (0.75)	4.99 (1.27)
%CV	33.19	26.68	27.15	12.97	25.40
Geometric mean	5.86	5.79	6.04	5.77	4.84
Median	6.19	5.89	6.00	5.79	4.63
Range	3.75 - 9.22	2.57 - 9.38	3.17 - 9.11	4.94 - 6.71	3.17 - 6.37
T_{max} (hr)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	3.75 (2.76)	3.72 (2.50)	4.04 (2.79)	4.25 (1.89)	5.00 (2.00)
%CV	73.64	67.08	68.94	44.54	40.00
Geometric mean	3.28	3.17	3.54	3.98	4.61
Median	3.00	3.00	3.00	3.50	5.00
Range	0.00 - 9.00	0.00 - 11.00	0.00 - 10.00	3.00 - 7.00	2.00 - 8.00
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	0.11 (0.07)	0.56 (1.03)	0.86 (1.17)	0.74 (0.59)	0.54 (0.12)
%CV	62.88	183.99	137.36	79.58	22.05
Geometric mean	0.10	0.31	0.60	0.54	0.53
Median	0.08	0.23	0.48	0.74	0.48
Range	0.08 - 0.25	0.13 - 6.00	0.17 - 6.00	0.23 - 1.25	0.48 - 0.75

(source: ov-1015-study-report-body.pdf, page 83/6880)

2.2.3. Transition from oral to IV administration: is the observed IV concentration decrease at 6 hours after infusion initiation on Day 7 (compared to steady-state oral concentration at 6 hours after an oral administration) clinically significant?

No, the decrease in Day 7 IV concentrations at 6 hours compared to oral concentration at 6 hours is not expected to result in worsening of efficacy from a clinical pharmacology perspective. Inclusion of patients receiving oral CBZ Q6h into labeling is acceptable.

On 06/12/2013, Sponsor submitted statistical bioavailability comparisons to the IND for Carbella (IND 073,686-0064). The results are presented in the table below.

Table 4: Statistical Bioavailability Comparisons Between Oral and IV CBZ for C_{max}, C_{min}, and AUC₀₋₂₄

Infusion Time ¹ Pharmacokinetic Parameter	IV Infusion		Oral		Ratio of Geometric LS Means ²	90% CI for Ratio
	Arithmetic Mean (%CV)	Geometric LS Mean	Arithmetic Mean (%CV)	Geometric LS Mean		
30 minutes (N=23)						
AUC(0-24) (µg.hr/mL)	186.40 (28.04)	178.99	204.58 (33.19)	192.74	0.929	(0.864, 0.998)
Cmax (µg/mL)	10.76 (34.91)	10.15	9.81 (33.74)	9.24	1.099	(1.010, 1.197)
Cmin (µg/mL)	6.28 (27.15)	6.04	7.21 (34.26)	6.77	0.892	(0.828, 0.961)
15 minutes (N=41)						
AUC(0-24) (µg.hr/mL)	180.08 (25.02)	174.25	191.45 (26.00)	184.48	0.945	(0.905, 0.986)
Cmax (µg/mL)	11.77 (34.42)	11.14	9.05 (24.85)	8.75	1.273	(1.174, 1.381)
Cmin (µg/mL)	6.01 (26.68)	5.79	6.71 (28.38)	6.43	0.900	(0.857, 0.944)
2-5 minutes (N=10)						
AUC(0-24) (µg.hr/mL)	179.42 (28.34)	172.60	189.85 (32.64)	179.68	0.961	(0.887, 1.041)
Cmax (µg/mL)	13.44 (50.98)	12.09	8.97 (31.47)	8.52	1.419	(1.062, 1.896)
Cmin (µg/mL)	6.18 (33.19)	5.86	6.57 (34.62)	6.19	0.947	(0.865, 1.037)

%CV = percent coefficient of variation; CI = confidence interval; LS = least-squares.

Note: Geometric LS means, ratio of geometric LS means, and 90% confidence interval for the ratio of geometric LS means are determined from a linear mixed effect model for the natural log transformed pharmacokinetic values with treatment as a fixed factor and subject as a random factor. Arithmetic means may differ from geometric LS means used for statistical analyses.

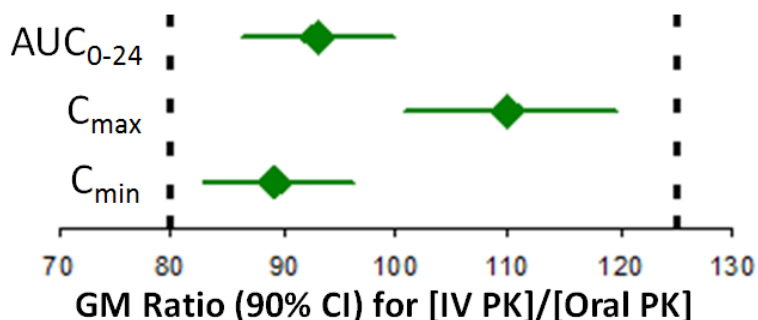
¹ Subjects in the 2-5-minute infusion group received 15-minute infusions on Day 1 through Day 7 and 2-5-minute infusions on Day 8; therefore, they are counted in both the 2-5-minute infusion and 15-minute infusion groups. Bioequivalence assessment for 2-5-minute infusions was not a primary objective of the study.

² IV Dose to Oral Dose Ratio (multiply by 100 to give percent).

(source: IND 073686-0064, 1-6-2-background-info-for-fda-10jun2013, page 3/6)

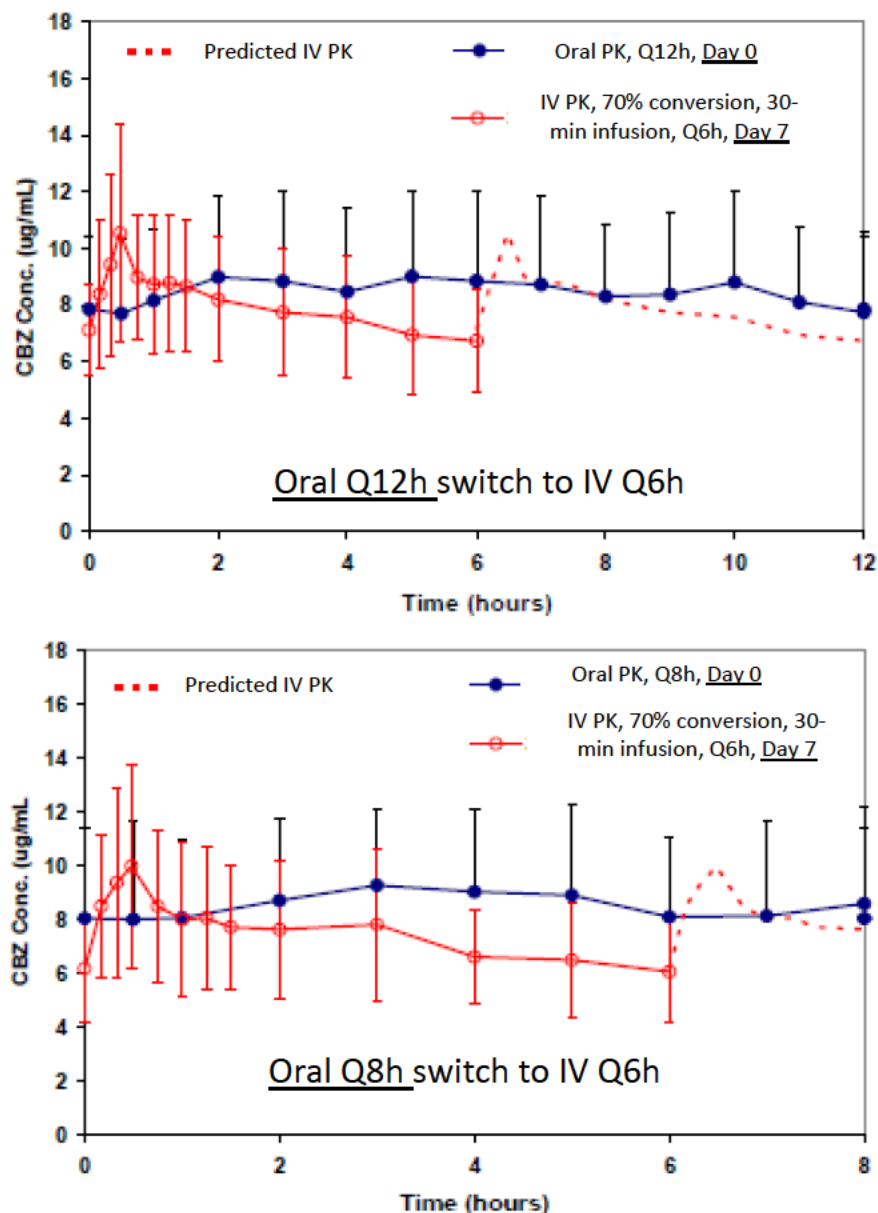
The analysis supported comparable exposures between oral and IV in terms of C_{max}, C_{min}, and AUC₀₋₂₄ for the 30-minute infusion, 70% oral-to-IV conversion, administered q6h. The results for the 30-minute infusion duration in the table above are presented as a forest plot in the figure below.

Figure 3: Geometric Mean Ratio and 90% Confidence Interval for IV PK Compared with Oral PK from Study OV-1015 for the 30-Minute Infusion



Conclusion: The results in Table 4 and Figure 3 indicate that the AUC₀₋₂₄, C_{max}, and C_{min} after 7 days of IV administration are comparable to those of oral administration. However, a comparison of the mean PK profiles during oral CBZ therapy compared to Day 7 of IV CBZ therapy showed that the IV PK profile drops below the “corresponding” oral PK profile during a time period of about 1-6 hours after the infusion initiation (see the figure below).

Figure 4: Comparison of Observed Oral PK (Day 0, Blue) With Observed IV PK (Day 7, Red) Expressed as Mean $\pm$ SD For Oral Q12h Patients (Top Panel) and Oral Q8h Patients (Bottom Panel) in Study OV-1015



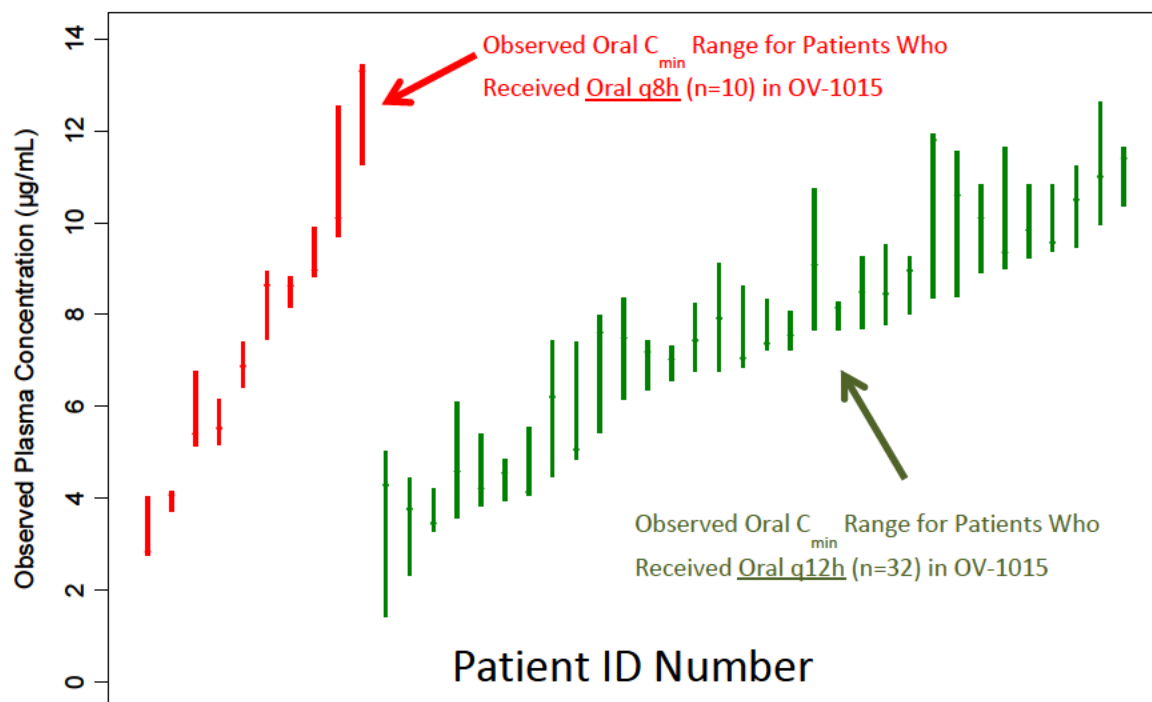
Based on literature searches and internal discussions, this reviewer concluded that there is no established information regarding the exposure-efficacy relationship for the CBZ anticonvulsant effect. Overall, the available literature did not provide an adequate exposure-response characterization in order to interpret the clinical significance of the observed concentration drop (~ 2 $\mu\text{g/ml}$ at 6 hr) in the figure above. As such, the reviewer's analyses focused on assessing the significance of this concentration drop resulting from the switch from oral to IV administration.

“Worst-Case Scenario” Decrease in CBZ Exposure (C_{6h} , Day 7). Since the exposures achieved by IV CBZ infusions tended to decrease day-to-day throughout the 7-day infusion regimen applied in study OV-1015, IV C_{6h} (e.g. IV C_{min}) values after 7 days of IV infusion are expected to be the lowest exposures achieved during the entire IV treatment period. For this reason, the IV C_{6h} values after 7 days of IV infusion (“worst-case scenario” where IV exposures are at a minimum) were compared to the oral C_{6h} during steady-state oral CBZ therapy.

Within each patient, the $C_{6h,IV}$ is about $2 \pm 2 \mu\text{g/mL}$ lower on average than $C_{6h,oral}$ (when switching from Q8h oral). In addition, the $C_{6h,IV}$ is about $2 \pm 1.4 \mu\text{g/mL}$ lower on average than $C_{6h,oral}$ (when switching from Q12h oral) within each patient. The distribution of intrasubject differences in $C_{6h,IV}$ and $C_{6h,oral}$ is shown in the boxplots in Figure 15 of section 4.1.2. This intrasubject decrease in C_{6hr} was compared to intrasubject variability in CBZ oral PK.

There is insufficient PK data to assess the intrasubject variability at the 6-hour time point for q8h oral PK and q12h oral PK (as the Sponsor only collected 12 hours of dense PK samples during oral therapy, on Day 0). However, since the Sponsor collected PK samples of oral C_{min} values at -14 days, -1 day, and on Day 0, (just prior to 9 am oral dose administration), the intra-subject oral PK variability was assessed in terms of C_{min} . The figure below shows the range and median CBZ C_{min} values observed while patients were on steady-state oral CBZ.

Figure 5: Observed Oral C_{min} Median and Range Across Days -14, -1, and 0 for Patients Receiving Oral Q8h CBZ (Red Lines) and Oral Q12h CBZ (Green Lines) Who Ultimately Switched to 70% Oral-to-IV Conversion, 30-minute Infusions, Q6h in Study OV-1015.



Each vertical line shows the max (top of line), median (point on line), and min (bottom of line) oral C_{min} concentration measured at 9 am on Days -14, -1, and 0 within an individual patient in study OV-1015. The 10 red bars on the left side represent patients who originally received oral q8h CBZ and switched to 30-minute IV

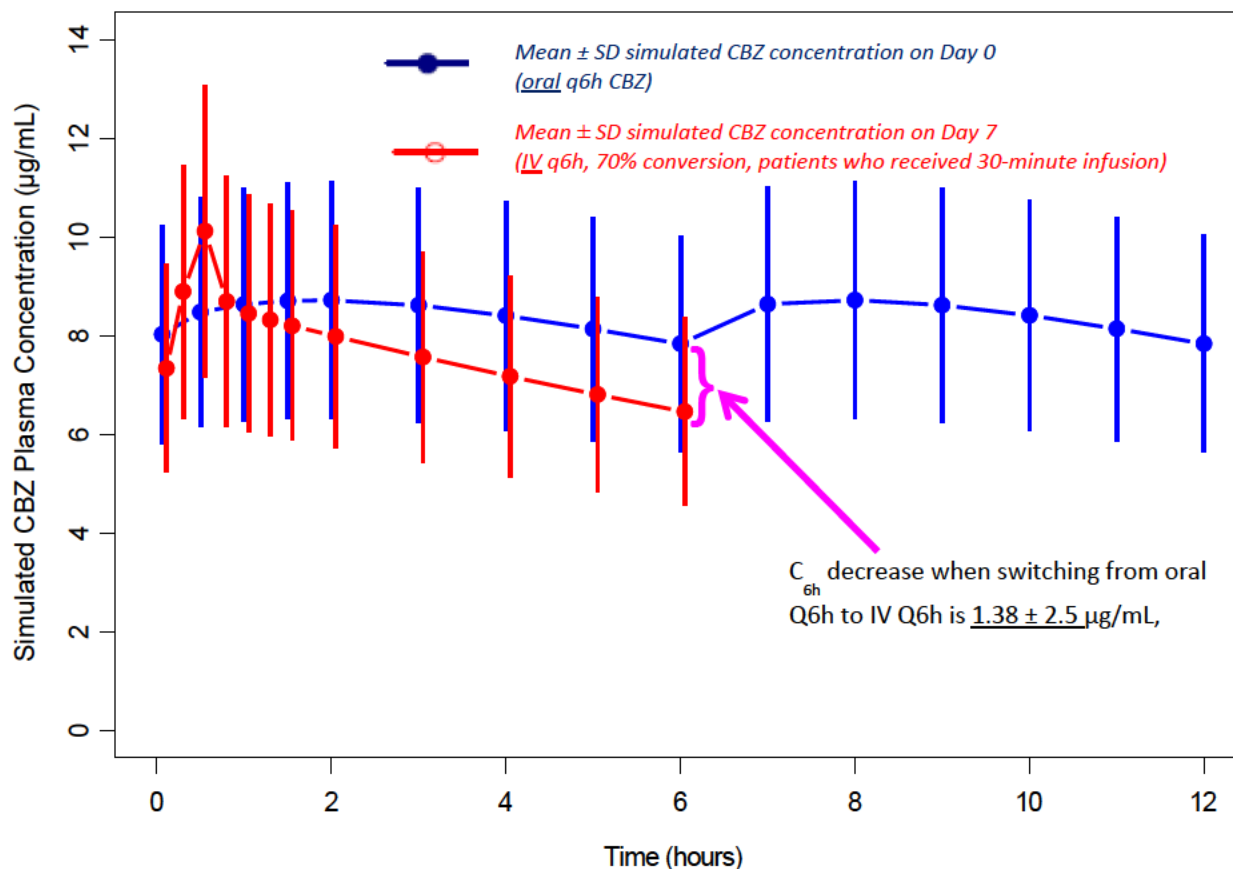
infusions. The 32 green bars on the right represent patients who originally received oral q12h CBZ and switched to 30-minute IV infusions

Though patients were at steady-state, the mean intrasubject oral CBZ C_{min} fluctuation over the 2-week period was 1.7 ± 0.8 $\mu\text{g/mL}$. The CBZ concentration decrease due to the “worst-case scenario” (Day 7 IV C_{6h}) is comparable to the intrasubject variability in oral C_{min} for patients receiving oral Q12h and oral Q8h CBZ (2 ± 2 and 2 ± 1.4 $\mu\text{g/mL}$, respectively).

Since CBZ-epoxide (CBZ-E) is an active metabolite, a similar comparison was made for the “total CBZ” (CBZ concentration + CBZ-E concentration). Over the 2-week period during oral steady-state, the mean intrasubject oral C_{min} fluctuation in total CBZ over the 2-week period was 2.01 ± 0.98 $\mu\text{g/mL}$. The total CBZ concentration decrease due to the Day 7 “worst-case scenario” in patients receiving oral Q12h and oral Q8h (2.34 ± 2.5 $\mu\text{g/mL}$ and 2.73 ± 1.57 $\mu\text{g/mL}$, respectively) was comparable to the mean intrasubject oral C_{min} variability for total CBZ.

Since there was only $n=1$ patient that received oral Q6h CBZ, the “worst-case scenario” for oral q6h was assessed using PK simulations. In order to simulate oral Q6h PK, data from other patients enrolled in the trial were utilized. In particular, PK parameters for oral q8h CBZ were estimated. The doses received by the oral q8h patients were utilized in the PK simulations of an oral q6h regimen. Patients receiving oral q12h (extended-release) CBZ were excluded from these analyses. The simulated oral q6h PK profile is shown in the figure below.

Figure 6: Mean $\pm$ SD Simulated Steady-State Oral PK Concentration Profile for Oral Q6h (Day 0) and Simulated IV PK Profile (Day 7) for After 7 Days of 70% Oral-to-IV Conversion, 30-Minute Infusion, Q6h.



Based on the PK simulations, the C_{6h} decrease when switching from oral Q6h to IV Q6h is $1.38 \pm 2.5 \mu\text{g/mL}$. Thus, the predicted C_{6h} decrease when switching from oral Q6h is comparable to the C_{6h} decrease observed for patients when switching from oral q12h, or oral q8h.

Since the observed intra-subject oral C_{min} fluctuations were of a comparable magnitude to the observed “worst-case scenario” decrease when switching to IV (decrease in Day 7 IV C_{6h} compared to Day 0 oral C_{6h}) for carbamazepine as well as total CBZ (the sum of CBZ and CBZ-E), transitioning to 70% oral-to-IV conversion, 30-minute infusion, Q6h is not expected to result in a worsening of efficacy from a clinical pharmacology standpoint. This finding is reasonable as CBZ PK after oral administration is expected to display greater variability than CBZ PK after IV administration. In addition, the current Tegretol label provides the following statements regarding different dosage forms and dosing intervals:

- “Conversion of patients from oral Tegretol tablets to Tegretol suspension: Patients should be converted by administering the same number of mg per day in smaller, more frequent doses (i.e., b.i.d. tablets to t.i.d. suspension).”
- “Increase [dose] at weekly intervals by adding up to 200 mg/day using a b.i.d. regimen of Tegretol-XR or a t.i.d. or q.i.d. regimen of the other formulations until the optimal response is obtained.”

*The above directions suggest that CBZ therapy can provide adequate effectiveness for b.i.d., t.i.d., or q.i.d intervals. In addition, the **PK simulations demonstrate that it is acceptable to include patients receiving oral q6h into the Carbella label.** The medical officer should comment on these findings.*

The reviewer also assessed

(b) (4)

here are also CMC issues regarding insufficient information regarding leachable and extractable components (due to Captisol) with the 70% formulation. At the time that this review was archived, these issues were unresolved and an outstanding CMC information request regarding these concerns was not yet answered (please see the CMC review by Dr. Shastri Bhamidipati for details and updates regarding the CMC issues).

*Also, the reviewer assessed the effect of a q4h infusion interval on PK. However, discussions with the medical officer have led to the understanding that administering Carbella more frequently (e.g. q4h instead of q6h) was not practical from a hospital logistics standpoint. For these reasons, **the regimen that must be proposed for the label is 70% oral-to-IV conversion, 30-minute infusion, administered Q6h.***

(b) (4)

2.2.4 Is the transition from IV CBZ to oral CBZ acceptable?

The Sponsor proposes to transition directly back to oral CBZ after the IV CBZ is complete. The safety of transitioning back from IV to oral CBZ was assessed by examining the seizure frequency data before, during, and after IV CBZ therapy from studies OV-1015 and 13181a. Study OV-1015 demonstrated a worsening of seizure frequency after returning to oral CBZ (0.4 to 0.6 seizures per week for IV and subsequent oral phase), whereas study 13181a demonstrated lower seizure frequency after returning to oral CBZ (2.5 and 1.4 seizures per week for IV and subsequent oral phase). However, overall, the mean seizure frequency after transitioning back to oral CBZ is lower than the mean seizure frequency documented previously on oral CBZ (see the tables below).

Table 5: Seizure frequency prior to IV treatment, during IV treatment, and after IV treatment in study OV-1015 (PK study).

	Pre IV Day -28 to Day 0	IV Day 1 to Day 7	Post IV Day 8 to Day 38
30-minute infusion (n)	43	43	41
Mean (SD)	1.0 (2.4)	0.4 (1.0)	0.6 (1.5)
Range	0.0 - 13.5	0.0 - 4.0	0.0 - 7.9
15-minute infusion (n)	43	43	41
Mean (SD)	1.6 (6.0)	1.2 (2.8)	1.2 (4.2)
Range	0.0 - 34.1	0.0 - 16.0	0.0 - 24.3
Total (n)	86	86	86
Mean (SD)	1.3 (4.6)	0.8 (2.1)	0.9 (3.2)
Range	0.0 - 34.1	0.0 - 16.0	0.0 - 24.3

(source: ov-1015-study-report-body.pdf, page 116/6880)

The following table indicates that seizure frequency did not increase after switching from IV CBZ back to the patient's original oral CBZ regimen in study 13181a (safety study).

Table 6: Seizure frequency prior to IV treatment, during IV treatment, and after IV treatment in study 13181a (Safety Study, No PK Collected)

		Pre-IV	IV	Post-IV
Number of Patients		105	105	105
Weekly Seizure Rate	N	105	105	102
	Mean	1.7	2.5	1.4
	Median	0	0	0
	SD	4.09	8.68	3.73
	Min	0	0	0
	Max	35	65	32
Change from Baseline	N		105	102
	Mean		0.8	-0.3
	SD		6.30	1.93
	Min		-8	-11
	Max		46	7
	Median		0	0

(source: 13181a-study-report-body.pdf, page 203/655)

The table above demonstrates that seizure frequency increased during IV CBZ treatment (80% increase from baseline) then returned to a level that was 30% lower than baseline. The reason for the worsening of seizure frequency during IV treatment period is not clear. PK samples were not collected in study 13181a.

Results from studies OV-1015 and 13181a are not consistent. However, the seizure frequency change is not considered significant. Transitioning directly from IV CBZ to oral CBZ appears acceptable. Please see the clinical review by Dr. Steven Dinsmore for more information regarding seizure frequency observed during the trial.

2.3. Intrinsic Factors

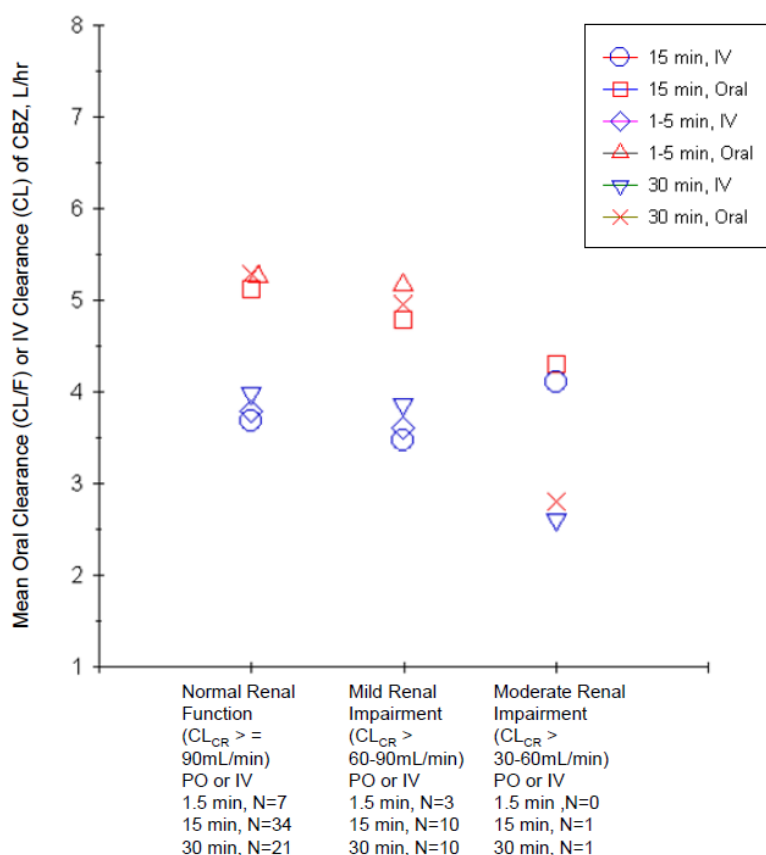
2.3.1. Do Patients with renal impairment require a dose adjustment?

2.3.1.1. Carbamazepine

No, patients with renal impairment do not require a CBZ dose adjustment. The label for CBZ products indicates that the effect of renal impairment on CBZ pharmacokinetics is not known. Patients entered study OV-1015 on a steady-state CBZ dose that is presumably tolerable and efficacious. As such, any dose adjustments due to renal impairment were previously implemented when patients initiated CBZ oral therapy.

The Sponsor provided analyses estimating the CBZ CL after IV administration and CBZ CL/F following oral administration. The clearance values are stratified by renal status as well as infusion duration in the figure below.

Figure 7: Mean CL/F of CBZ for Normal Renal Function and Renal Impairment After IV and Oral CBZ Administration in Study OV-1015

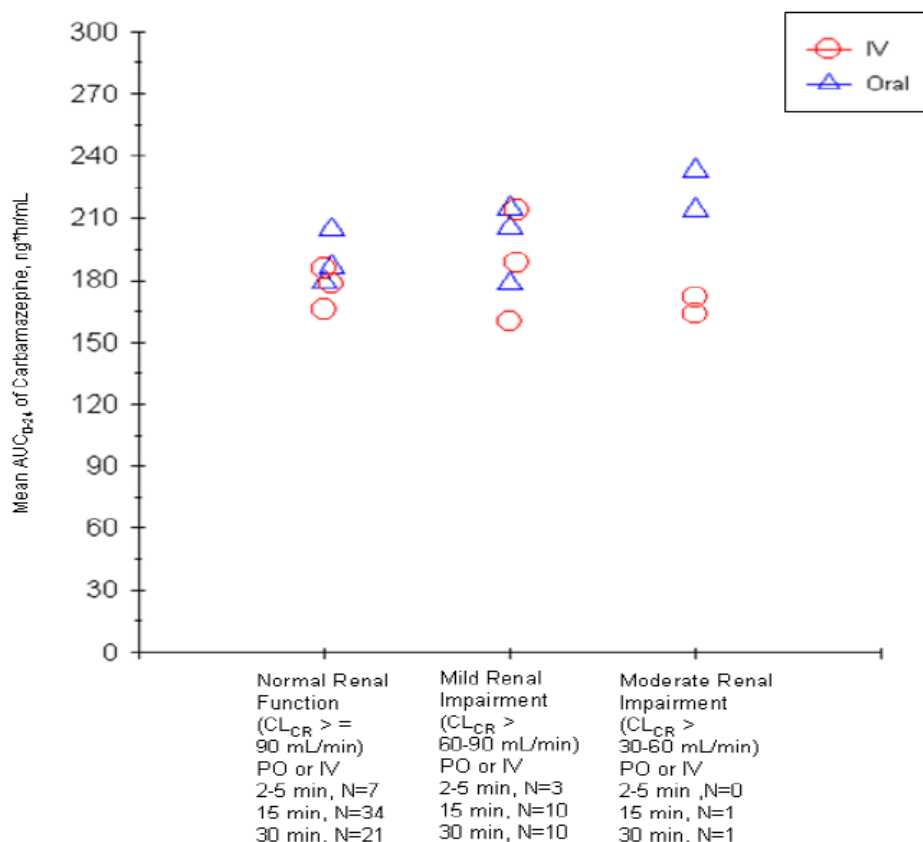


(source: *clin-pharm-review-aid.pdf*, NDA 206030, page 23/45)

Patients with normal renal function ($n=62$; $n=7$ received 2-5 minute infusions, $n=34$ received 15 minute infusions, and $n=21$ received 30 minute infusions) as well as patients mild renal impairment ($n=23$; $n=3$ received 2-5 minute infusions, $n=10$ received 15 minute infusions, and $n=10$ received 30 minute infusions) demonstrated lower IV CL compared to oral CL/F. However, when considering the mean bioavailability estimate of 70%, the difference between IV CL and oral CL/F becomes insignificant. The CL/F values between normal renal patients and patients with mild renal impairment are comparable. Also, the IV CL is comparable between patients with normal renal function and patients with mild renal impairment.

There were $n=2$ patients with moderate renal impairment ($n=1$ received a 15 minute infusion, and $n=1$ received a 30-minute infusion). It is unclear why the oral CL/F and IV CL are highly similar for both patients. The effect of renal function on CBZ AUC after oral and IV CBZ administration is presented in the figure below.

Figure 8: Mean AUC₀₋₂₄ of CBZ for Normal Renal Function and Renal Impairment After IV and Oral CBZ Administration in Study OV-1015



(source: pre-NDA meeting background materials, IND 073,686, page 25/234)

The mean AUC₀₋₂₄ is comparable between patients with normal renal function and mild renal function. Within the group of patients with normal function and as well as the group of patients with mild renal impairment, IV CL was comparable to oral CL/F. Variability of IV CL and oral CL/F is consistent with CBZ PK variability.

The small sample size (n=2) of patients with moderate renal impairment (n=2) and lack of patients with severe hepatic impairment precludes a meaningful assessment of the effect of moderate to severe renal impairment on CBZ pharmacokinetics.

The data suggest that, when switching from oral to IV CBZ, patients with mild renal impairment do not require a CBZ dose adjustment. The effect of moderate or severe renal impairment on CBZ PK is not known.

2.3.2.2. Captisol

No, a Captisol dose adjustment is not needed for patients with mild renal impairment. Carbella use is not recommended in patients with moderate and severe RI as well as patients with ESRD. Details of the Captisol pharmacokinetics can be found in the table below.

Table 7: Captisol PK after IV Administration on Day 1 and Day 7 in Patients with Normal Renal Function and Mild Renal Impairment

	Normal Renal Function			Mild Renal Impairment		
Weight (kg)	93.1 (20.1)			64.2 (6.2)		
	Day 1 (n=15) Mean (% CV)	Day 7 (n=16) Mean (% CV)	7-Day Accumulation	Day 1 (n=9) Mean (% CV)	Day 7 (n=9) Mean (% CV)	7-Day Accumulation
Dose (mg)	5192 (13.8)	5195 (13.4)		3840 (27.8)	3840 (27.8)	
Dose (mg/kg)	58.8 (24.4)	58.1 (24.4)		59.9 (27.4)	59.9 (27.4)	
C _{max} (µg/mL)	520 (22.9)	551 (26.2)	1.061 (23)	478 (30.4)	491 (32.5)	1.031 (16)
AUC _{0-tau} (µg*hr/mL)	720 (25.5)	830 (28.3)	1.128 (14)	741 (28.7)	837 (27.5)	1.141 (11)
CL (L/h)	6.96 (20.3)	6.73 (31.7)		4.89 (21.0)	4.67 (19.3)	
CL (L/hr/kg)	0.078 (29.0)	0.0747 (31.8)		0.076 (21.6)	0.073(19.5)	
V _z	14.9 (19.6)	14.6 (20.2)		11.2 (11.3)	11.9 (9.2)	
V _z (L/hr/kg)	0.166 (20.3)	0.0161 (22.4)		0.175 (8.7)	0.185 (7.2)	
T _{1/2} (hr)	1.53 (29.7)	1.55 (15.8)		1.64 (17.9)	1.82 (20.4)	

The table above indicates that patients with normal renal function demonstrate 7-day Captisol accumulation that is comparable to patients with mild renal impairment (for both C_{max} and AUC_{0-tau}). Though there is an 11% reduction in Captisol CL/kg in patients with mild RI compared to patients with normal renal function, this difference is not expected to be clinically significant. **No Captisol dose adjustment is required for patients with mild renal impairment.**

The Sponsor did not provide data in patients with severe renal impairment and only provided n=2 patients with moderate renal impairment. However, according to the current label (04/07/2014) for VFEND (voriconazole solution containing Captisol), in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. As a result, the label states that intravenous VFEND administration should be avoided in patients with moderate to severe renal impairment. In

*addition, the daily Captisol dose in Carbella (e.g. up to 28000 mg Captisol/day for doses up to 1600 mg oral CBZ / day) can exceed that Captisol dose in than Vfend (13440 mg Captisol/day for Vfend loading dose, 8960 mg Captisol for Vfend maintenance dose). **For this reason, use of Carbella in patients with moderate and severe renal impairment and ESRD is not recommended.***

***NAG Increase:** The mean change from baseline at steady state N-acetyl-β-D-glucosaminidase (NAG) is increased 53% (U/mmol creatinine) over the baseline mean in study 13103A. In addition to the population increase, an increase in NAG is indicative of damage to renal tubules. Please refer to the clinical review of NDA 206030 (Dr. Steven Dinsmore) for information regarding the clinical implications of these findings.*

2.3.2. Do Patients with hepatic impairment require a dose adjustment?

The current submission does not contain any studies assessing the effects of hepatic impairment on pharmacokinetics of CBZ or Captisol.

2.3.2.1. Carbamazepine

According to the current labels for CBZ products, the effects of hepatic impairment on CBZ pharmacokinetics are not known. The current advice from the Carbatrol label is to proceed with caution when using Carbatrol in patients with hepatic dysfunction.

*The current submission does not provide data to assess the effect of switching to IV on patients with hepatic impairment. As such, it is not clear whether patients with hepatic impairment may experience elevated concentrations when switching from oral to IV administration (in comparison to patients with normal hepatic function) due to the elimination of a first-pass effect. **For these reasons, similar to oral CBZ, Carbella should be used with caution in patients with impaired hepatic function.***

2.3.2.2. Captisol

Renal elimination is the major route of elimination for Captisol. Currently, per the approved products which contain Captisol, Vfend, Geodon, Abilify, and Nexterone, there is no evidence to demonstrate an effect of hepatic impairment on Captisol PK.

2.4 Extrinsic Factors

2.4.1 What is the potential for DDI?

2.4.2.1. Carbamazepine

CBZ is a substrate of 3A4. Concomitant medications which induce or inhibit these enzymes can alter CBZ exposures. The label for Carbella will be consistent with information from the current Tegretol label, in regards to drug interactions regarding CBZ (see section 3).

2.4.2.2. Captisol

Renal elimination is the major route of elimination for Captisol. Currently, per the approved products which contain Captisol, Vfend, Geodon, Abilify, and Nexterone, there is no evidence to demonstrate the DDI potential with Captisol.

2.5. General Biopharmaceutics

2.5.1. Are the proposed infusion durations of (b) (4) 30-minutes acceptable?

The Sponsor proposed to utilize (b) (4) a 30-minute infusion duration. However, adverse event rates were higher for various adverse events (e.g. dizziness, headache, and somnolence) for patients receiving the 15-minute infusion compared to the 30-minute IV infusion (See Table 21 in section 4.1.2). In addition, the 30-minute infusions were associated with lower C_{max} values, and comparable C_{min} values compared to the 15-minute infusion (see Figure 13 and 14 in section 4.1.2). For these reasons, the 30-minute infusion duration is recommended.

2.6. Analytical

2.6.1. Concentration Measurements

2.6.1.1. PK sample collection schedule

Study OV-1015: Sponsor collected frequent PK samples for us to 6 hours after the first infusions on Days 1 and 7. For other infusions, PK samples were acquired pre-infusion and end of infusion. See section 4.1.1 in the appendix for additional details.

2.6.1.2. What bioanalytical methods were used?

Study OV-1015: Sponsor utilized LC-MS/MS methods to quantify CBZ, CBZ-epoxide, and Captisol plasma concentrations in study OV-1015.

2.6.1.3. Were the analytical methods utilized in study OV-1015 adequately validated?

Yes. The following table summarizes the Sponsor's analytical method validation data for all analytes measured in study OV-1015.

Table 8: Bioanalytical Validation Data for CBZ LC-MS/MS Method (Study OV-1015)

Information Requested	Data
Analyte	Carbamazepine
Internal standard (IS)	Carbamazepine-d ₁₀
Limit of quantitation	0.05 µg/mL
Average recovery of drug (%)	90.9, 99.1, 102 for QC1, QC3, QC5
Average recovery of IS (%)	90.1
Standard curve concentration	0.05, 0.1 0.2 0.8 3, 12, 40, 50 µg/mL
Standards accuracy range (%)	-3.84% to 6.22%
Standards precision range (%)	3.94% to 6.71%
QC range	0.15, 0.4, 1.5, 6, 9, 37.5 µg/mL
QC precision range (%)	2.58% to 9.48%
QC accuracy range (%)	-4.82% to 12.7%
Bench-top stability (hrs)	24.75 hours
Stock stability (days)	1120 days
Post-preparative stability (hrs)	102 hours at room temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	15 days at -20°C
Dilution integrity	100 µg/mL diluted 5-fold
Selectivity	No significant interference from chromatographic peaks detected in blank plasma

(source: aeel2-report.pdf, page 18-36 of 137)

Table 9: Bioanalytical Validation Data for CBZ-Epoxide LC-MS/MS Method (Study OV-1015)

Information Requested	Data
Analyte	Carbamazepine 10,11-Epo
Internal standard (IS)	Carbamazepine-10,11-Epo
Limit of quantitation	0.05 µg/mL
Average recovery of drug (%)	90.3%, 93.5%, and 97.2% for QC1,2, and 3
Average recovery of IS (%)	94.7%
Standard curve concentration	0.05, 0.1, 0.2, 0.8, 3, 12, 40, 50 µg/mL
Standards accuracy range (%)	-3.76% to 3.67%
Standards precision range (%)	3.79% to 7.37%
QC range	0.05, 0.15, 0.4, 1.5, 6, 37.5 µg/mL
QC precision range (%)	3.34% to 6.36%
QC accuracy range (%)	-0.294% to 3.38%
Bench-top stability (hrs)	24.75 hours
Stock stability (days)	1094 Days
Post-preparative stability (hrs)	102 hours at room temperature
Freeze-thaw stability (cycles)	Four cycles
Long-term storage stability (days)	15 days at -20°C
Dilution integrity	100 µg/mL diluted 5-fold
Selectivity	No significant interference from chromatographic peaks detected in blank plasma

(source: aeel2-report.pdf, page 40 of 137)

Table 10: Bioanalytical Validation Data for Captisol LC-MS/MS Analytical Method (Study OV-1015)

Information Requested	Data
Analyte	Captisol
Internal standard (IS)	Captisol-G (Sulfobutyl ether gamma-cyclodextrin)
Limit of quantitation	5 µg/mL
Average recovery of drug (%)	123.9%, 100.7% for QC-L and QC-H
Average recovery of IS (%)	114%
Standard curve concentration	5, 10, 20, 40, 80, 120, 160, 200 µg/mL
Standards accuracy range (%)	96.7 – 104.5%
Standards precision range (%)	≤ 14.5%
QC range	15, 75, 150 µg/mL
QC accuracy range (%)	92.1-113.2% intra-run, 102.1-106.4% inter-run
QC precision range (%)	≤ 14.9% intra-run, ≤ 13.5% inter-run
Bench-top stability (hrs)	3.5 hours
Stock stability (days)	56 days at -20°C
Post-preparative stability (hrs)	29 hours
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	≤ -70°C for 28 days
Dilution integrity	5-fold and 20-fold dilution
Selectivity	No matrix interference was noted in blank plasma samples from six individuals.

(source: 64743-report.pdf, page 25 of 82)

Table 11: Inter-assay Precision and Accuracy of CBZ Assay (Study OV-1015)

Parameter	Range
Precision	4.84% to 7.86%
Accuracy	-3.51% to 1.73%

(source: aeoo-report-part-1of-2.pdf, page 316 of 2500)

Table 12: Inter-assay Precision and Accuracy of CBZ-Epoxyde Assay (Study OV-1015)

Parameter	Range
Precision	6.5% to 8.12%
Accuracy	-1.44% to 0.211%

(source: aeoo-report-part-1of-2.pdf, page 619 of 2500)

Table 13: Inter-assay Precision and Accuracy of Captisol Assay (Study OV-1015)

		Nominal Concentration of Captisol						Acceptance Ratio ^a
		QC-L		QC-M		QC-H		
		15.0 ug/mL		75.0 ug/mL		150 ug/mL		
		Measured Conc.		Measured Conc.		Measured Conc.		
File Name	Replicate	ug/mL	Acc.	ug/mL	Acc.	ug/mL	Acc.	
AQD 06112009DF (ISR)	1	21.2 ^b	141.4% ^b	57.1 ^b	76.1% ^b	156	103.9%	9/12
	2	22.3 ^b	148.7% ^b	77.6	103.4%	140	93.4%	
	3	17.1	114.0%	64.7	86.3%	129	85.7%	
	4	13.6	90.6%	76.6	102.1%	144	95.7%	
	MEAN	18.6	123.7%	69.0	92.0%	142	94.7%	
	SD	4.0		9.8		11		
	% CV	21.5		14.3		7.9		
	n	4		4		4		
	Acceptance Ratio ^a	2/4		3/4		4/4		

^a Acceptance Ratio = Acceptable QC samples / Total QC samples.

^b Value is outside the acceptance criteria of $\pm 15.0\%$ Acc of the nominal concentration.

Acceptance criteria = 2/3 of QCs pass overall and 50% at each level

(source: 64731-report.pdf, page 198 of 203)

3. Labeling Recommendations

The CARBELLA label provided by the Sponsor has been re-designed by the review team. For this reason, the Sponsor's label is not provided in this review. The following sections have been built using information from previous labels as well as the Sponsor's provided label.

2 DOSAGE AND ADMINISTRATION

2.1

(b) (4)

(b) (4)

Table 14. Determination of Dose for CARBELLA Infusion.

Total Daily Oral Carbamazepine Dose (mg/day)	(b) (4)	(b) (4)
	(mg/day)	every 6 hours
400	280	70
600	420	105
800	560	140
1,000	700	175
1,200	840	210
1,400	980	245
1,600	1,120	280

(b) (4)

(b) (4)

7 DRUG INTERACTIONS

7.1 (b) (4)

Carbamazepine is a potent inducer of hepatic CYP1A2, 2B6, 2C9/19 and 3A4 and may (b) (4) reduce plasma concentrations of (b) (4) mainly metabolized by CYP 1A2, 2B6, 2C9/19 and 3A4 through induction of their metabolism.

(b) (4)

Effects of Carbamazepine on Other Drugs

Concomitant Drug Name	Effect of Carbamazepine on Other Drugs	Clinical Recommendation
boceprevir	Decrease in concomitant drug levels	Boceprevir label <i>contraindicates</i> (b) (4)
acetaminophen, albendazole, alprazolam, aprepitant, buprenorphine, bupropion, citalopram, clonazepam, clozapine, corticosteroids (e.g. prednisolone, dexamethasone), cyclosporine, dicumarol, dihydropyridine calcium channel blockers (e.g. felodipine), doxycycline, ethosuximide, everolimus, haloperidol, imatinib, itraconazole, lamotrigine, levothyroxine, methadone, methsuximide, mianserin, midazolam, olanzapine, oral and other hormonal contraceptives, oxcarbazepine, paliperidone, phensuximide, phenytoin, praziquantel, protease inhibitors, risperidone, sertraline, sirolimus, tadalafil, theophylline, tiagabine, topiramate, tramadol, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline), valproate, warfarin, ziprasidone, zonisamide.	Decrease in concomitant drug levels	monitoring of concentrations (b) (4) dosage adjustment of the concomitant (b) (4)
cyclophosphamide	Increase in Cyclophosphamide levels (potential for increased toxicity)	Monitor for signs of increased cyclophosphamide toxicity
aripiprazole	Decrease in aripiprazole levels	When carbamazepine is added to aripiprazole (b) (4), the aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.
tacrolimus	Decrease in tacrolimus levels	monitoring of tacrolimus blood concentrations and appropriate dosage adjustments
temsirolimus	Decrease in temsirolimus levels	The use of concomitant strong CYP3A4 inducers such as carbamazepine should be avoided with temsirolimus. (b) (4) if (b) (4) must be coadministered carbamazepine with temsirolimus, (b) (4)
lapatinib	Decrease in lapatinib levels	The use of carbamazepine with lapatinib should generally be avoided. Dosage adjustment should be considered if lapatinib is coadministered with carbamazepine. (b) (4) is started in a patient already taking lapatinib, (b) (4) should be gradually titrated up. If carbamazepine is discontinued, the lapatinib dose should be reduced.
nefazodone	Decrease in nefazodone levels	Coadministration of carbamazepine with nefazodone is contraindicated
Valproate		Monitor concentrations valproate when (b) (4) is introduced or withdrawn in patients using valproic acid

Effects of Carbamazepine on Other Drugs (Continued)

Concomitant Drug Name	Effect of Carbamazepine on Other Drugs	Clinical Recommendation
Lithium	may increase the risk of neurotoxic side effects.	Use with intensive monitoring
Isoniazid	increase isoniazid-induced hepatotoxicity	
Diuretics (e.g. hydrochlorothiazide, furosemide)	may lead to symptomatic hyponatremia	
Hormonal Contraceptives (e.g., oral and levonorgestrel subdermal implant contraceptives)	may render the contraceptives less effective because the plasma concentrations of the hormones may be decreased. Breakthrough bleeding and unintended pregnancies have been reported	Alternative or back-up methods of contraception (b) (4).
Neuromuscular Blocking Agents (e.g. agents pancuronium, vecuronium, rocuronium, and cisatracurium)	Resistance to the neuromuscular blocking action of the non-depolarizing neuromuscular blocking agents	(b) (4) for more rapid recovery from neuromuscular blockade than expected, (b) (4) infusion (b) (4) may be higher

7.2 (b) (4)

CYP3A4 inhibitors inhibit (b) (4) metabolism and can thus increase plasma carbamazepine levels. CYP3A4 inducers can increase the rate of (b) (4) metabolism and thus decrease carbamazepine levels.

(b) (4)

Effects of Other Drugs on Carbamazepine

Concomitant Drug Name	Effect of Concomitant Drug on Carbamazepine	Clinical Recommendation
aprepitant, cimetidine, ciprofloxacin, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, fluvoxamine, trazodone, olanzapine, loratadine, terfenadine, omeprazole, oxybutynin, dantrolene, isoniazid, niacinamide, nicotinamide, ibuprofen, propoxyphene, azoles (e.g. ketoconazole, itraconazole, fluconazole, voriconazole), acetazolamide, verapamil, ticlopidine, grapefruit juice, protease inhibitors.	Increase in carbamazepine level (by CYP3A4 Inhibition)	Close monitoring of carbamazepine levels (b) (4) dosage adjustment may be required
cisplatin, doxorubicin HCl, felbamate†, fosphenytoin, rifampin, phenobarbital, phenytoin, primidone, methsuximide, theophylline, aminophylline.	Decrease in carbamazepine level (by CYP3A4 induction)	
loxapine, quetiapine and valproic acid	Increase in <i>metabolite</i> (carbamazepine-10,11-epoxide) levels (by inhibition of human microsomal epoxide hydrolase)	(b) (4)

8.6 Renal Impairment

(b) (4)

8.7 Hepatic Impairment

(b) (4)

12.3 Pharmacokinetics

Specific Populations

Renal Impairment:

Carbamazepine clearance was comparable between patients with normal renal function and patients with mild renal impairment (creatinine clearance 60-89 mL/min) for both oral carbamazepine and IV (b) (4). The effects of moderate and severe renal impairment (creatinine clearance 30-59 mL/min and 15-29 mL/min, respectively) on carbamazepine pharmacokinetics are not known.

(b) (4)

Hepatic Impairment:

The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. Patients with hepatic impairment may experience elevated concentrations when switching from oral to IV administration (in comparison to patients with normal hepatic function) due to reduction of the first-pass effect (see section 8.7).

14.1 Study to Demonstrate Comparable Carbamazepine Exposures Between Oral Carbamazepine to IV Carbella

In a sequential, open-label study n=98 adult patients receiving oral CBZ (Carbatrol, Tegretol, Tegretol XR) q6h (n=1), q8h (n=24), or q12 (n=73) at for epilepsy transitioned to IV CARBELLA. Patients received a total daily IV CARBELLA dose equal to 70% of their total daily steady-state oral dose. Patients were randomized to receive q6h CARBELLA with

infusion duration of 30-minutes, 15-minutes, or 2-5 minutes. Patients received CARBELLA for 7 days then switched back to their existing oral CBZ regimen.

Steady-state oral carbamazepine PK was compared to IV CARBELLA PK at steady state (defined as Day 7 of CARBELLA treatment). For patients that received the 30-minute infusions, C_{min} , C_{max} , and AUC_{0-24} after CARBELLA treatment were comparable with oral treatment. In addition, patients that received the 30-minute infusion duration presented lower adverse event rates, lower C_{max} values, and comparable C_{min} values compared to patients that received the 15-minute infusion.

However, the C_{min} for oral q8h and q12h carbamazepine occur at 8 and 12 hours after oral administration whereas CARBELLA C_{min} occurs at 6 hours after infusion. Within each patient, the CARBELLA C_{min} (6 hours after a 30-minute infusion on Day 7) was 2 µg/mL lower on average than the concentration 6-hours after an oral administration. However, in the same patient subset, a person's oral C_{min} value fluctuated 1.7 µg/mL on average over a 2-week period. The 2 µg/mL concentration decrease when switching from oral carbamazepine to CARBELLA is not expected to result in a worsening of efficacy since oral C_{min} fluctuations over a 2-week period were of a comparable magnitude (1.7 µg/mL).

CARBELLA was only studied in n=1 patient receiving oral carbamazepine q6h. However, pharmacokinetic simulations indicate that CARBELLA may be used in patients receiving oral carbamazepine q6h.

4. Appendices

4.1 Pharmacometric Review

4.1.1 Is the Sponsor's Population PK Model Acceptable?

Sponsor's Analyses:

Sponsor's final population PK model was a 2-compartment model with inter-individual variability terms on clearance, volume of distribution of compartment 1, and volume of distribution of compartment 2. The model was constructed using PK data from Day 7 in order to represent steady state CBZ kinetics.

Table 16: Summary of Modeling-Building Procedure for Population Pharmacokinetics of IV CBZ Infusions

Model	Compartments		Cl (L/hr)	V or Vc (L)	Q (L/hr)	Vp (L)	IRV CV%	Model Covariate	Objective	Condition Number Ratio
A	1	Estimate	3.37	48.9			15.7		1332	11.7
		SE%	4.4	4.5			8.3			
		IIV	33.9	19.9						
		SE%	17.1	37.0						
B	2	Estimate	3.47	5.83	271	59.7	7.07		365	30.5
		SE%								
		IIV	35.7	-	114.2	16.2				
		SE%								
C	2	Estimate	3.47	17.8	88.7	53.4	7.73		438	9.1
		SE%	4.5	13.4	5.7	6.2	8.1			
		IIV	35.8	93.4						
		SE%	18.7	21.6						
D	2	Estimate	3.47	16.3	93.8	45.3	7.08		402	13.9
		SE%	4.5	14.9	4.9	9.6	9.8			
		IIV	35.8	96.7		52.0				
		SE%	18.7	21.3		47.4				
E	2	Estimate	3.47	5.83	268	59.7			372	no
		SE%								
		IIV	35.7	0.5	112.3					
		SE%								
F	2	Estimate	3.47	16.4	93.0	41.3	7.07	Vc:Vp -0.443	371	68.2
		SE%	4.5	14.2	4.9	10.4	9.7	cor -0.734		
		IIV	35.9	94.5		57.4				
		SE%	18.8	20.6		3.9				
G	2	Estimate	3.47	5.83	271	59.7	7.07		365	13.6
		SE%	4.5	10.2	19.5	3.6	9.2			
		IIV	35.7		114.2	16.2				
		SE%	19.6		31.1	39.9				
H	2	Estimate	3.47	5.83	267.8	59.7	7.27		372	14.2
		SE%	4.5	10.1	20.0	3.4	7.9			
		IIV	35.6		112.3					
		SE%	18.7		32.1					

IRV = intra-individual residual variability for constant CV and additive error model

SE% = standard error of estimate as %; IIV = inter-individual variability as %

COV = covariance; Cor = correlation

The final model is Model F. Sponsor had one additional model (Model G) which produced a lower objective function (365). Model G was similar to Model F, except an inter-individual variability term was placed on Q, and the inter individual variability term was not present on V_c. However, Sponsor utilized model F as the final model since the mean Bayesian values for alpha were unrealistic ($77 \pm 90 \text{ hr}^{-1}$) and the Bayesian estimate for Q spanned a 5-fold range. The Sponsor provided the following diagnostic plots.

Figure 9: Population (PRED) and individual (IPRED) predicted CBZ plasma concentration versus observed plasma concentrations.

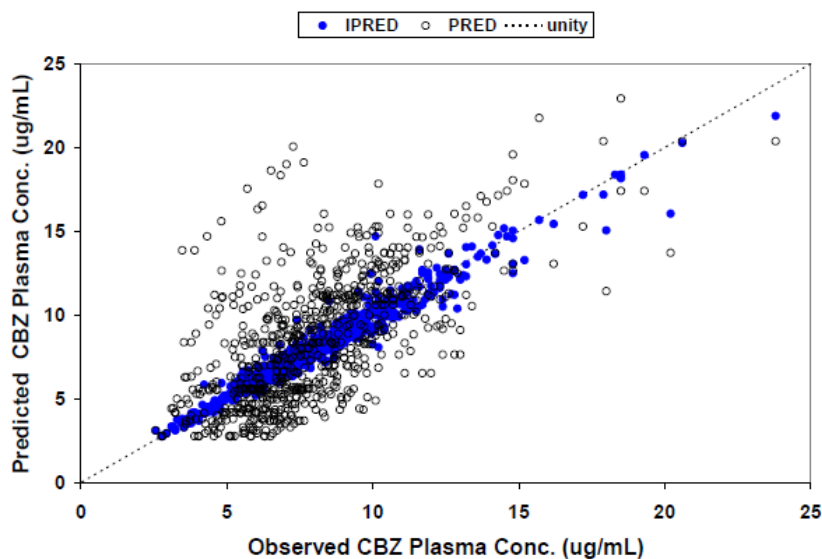
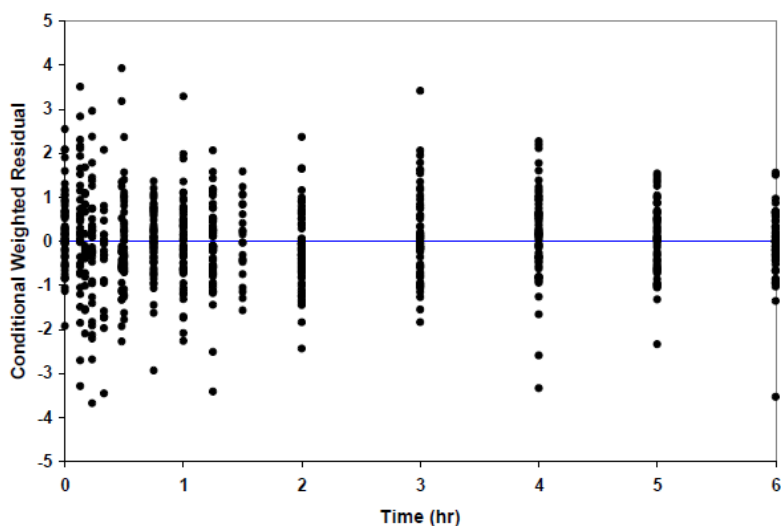
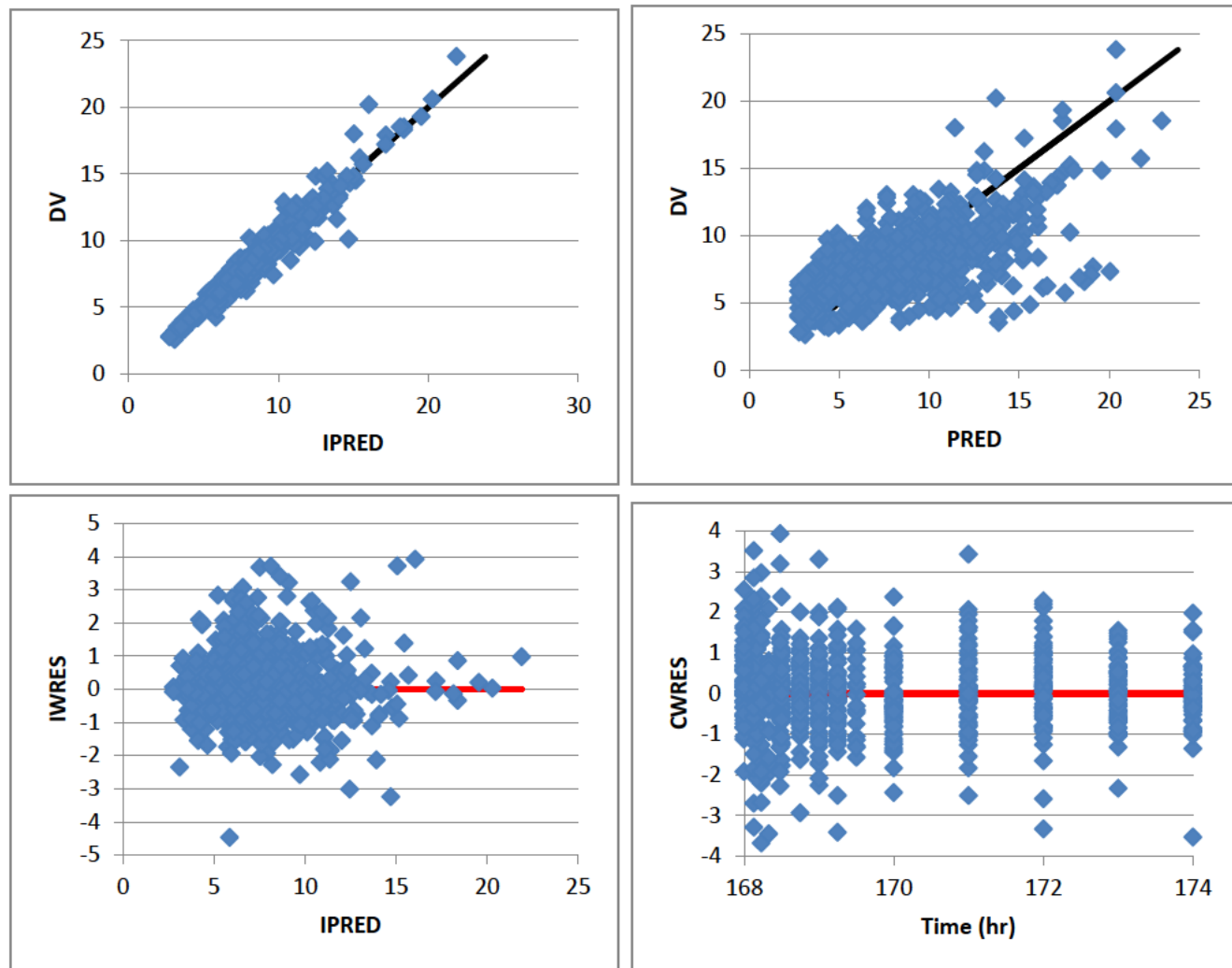


Figure 10: Conditional weighted residual versus time for CBZ plasma concentrations based on Model F



Reviewer analyses: The following diagnostic plots were generated by the reviewer.

Figure 11: Diagnostic plots for the Sponsor's Population Pharmacokinetics Model



DV represents observed CBZ concentration, IWRES is individual weighted residual, CWRES is conditional weighted residual, PRED is population predicted CBZ concentration, and IPRED is individual predicted CBZ plasma concentration.

The Sponsor's model-building procedure and final model selection are acceptable.

4.1.2 Transition from oral to IV administration: Is the observed IV concentration decrease at 6 hours after infusion initiation on Day 7 (compared to oral steady-state oral concentration at 6 hours after oral administration) clinically significant? (Appendix of additional analyses)

Sponsor originally submitted results of statistical PK comparisons between oral and IV routes from study OV-1015 on 06/12/2013 (IND 073,686-0064; see Table 4 in section 2.2.2). The 90% CI for the ratio of each CBZ PK parameter were contained within the 80-125% no-effect boundaries for AUC_{0-24} , C_{max} , and C_{min} for the group of patients who received 30-minute infusion durations. Patients who received the 15-minute and 2-5 minute durations presented point-estimates of C_{max} ratios which exceeded the no-effect boundaries.

Sponsor also provided a similar analyses for the metabolite, CBZ-epoxide (CBZ-E) as well as “total CBZ” (the sum of CBZ and CBZ-E). For CBZ-E, the 90% CI for ratios of PK parameters (AUC_{0-24} , C_{max} , and C_{min}) for all infusion durations (30, 15, and 2-5 minutes) fell below the 80% no-effect boundary. For “total CBZ”, the patients receiving 30-minute infusions, the 90% CI for ratios of all PK parameters were contained within the 80-125% no effect boundaries. However, patients that received 15-minute and 2-5 minute infusion durations had C_{max} ratios that were above the 125% boundary.

A pre-NDA meeting occurred on 09/10/2013. The key discussion points from the pre-NDA meeting are summarized below:

- The single patients receiving oral q6h CBZ does not support labeling for oral q6h patients
- Formal bioequivalence standards should be met when introducing a new formulation
- The difference in shape between oral q8h and IV q6h as well as oral q12h compared to IV q6h may affect efficacy and safety
- Due to differences in oral regimen and IV regimen, the Agency requested that the Sponsor conduct analyses of partial AUC (pAUC) as well as analyses of individual concentrations (similar to the approach that was applied to Trokendi®, an extended-release topiramate formulation). If one or more time points presented results that were outside of the no-effect boundaries, the Sponsor was asked to provide rationale for why safety and efficacy are not expected to be significantly affected.
- Additional approaches such as conducting a single-dose PK study (accounting for auto-induction) as well as an approach of PK/PD also discussed.

On 09/30/2013, the Sponsor submitted results (IND 073686-0067) of statistical PK analyses which included pAUC estimates and were stratified by infusion time as well as oral dosing interval (e.g. oral q8h patients were analyzed separately from oral q12h patients).

Table 17: Statistical Bioavailability Comparisons Between Oral and IV CBZ using pAUC

Infusion Time Pharmacokinetic Parameter	Oral Dosing Interval (hour)	IV Infusion		Oral		Ratio of Geometric	
		Arithmetic Mean (%CV)	Geometric LS Mean	Arithmetic Mean (%CV)	Geometric LS Mean	LS Means IV/Oral	90% CI for Ratio
30 minutes (N=17)							
AUC(0-2) (µg*hr/mL)	12	17.65(27.6)	16.98	16.50(31.5)	15.61	1.087	(0.999,1.183)
AUC(2-4) (µg*hr/mL)	12	15.63(28.0)	14.99	17.57(33.9)	16.51	0.908	(0.817,1.009)
AUC(4-6) (µg*hr/mL)	12	14.09(28.2)	13.52	17.67(33.7)	16.57	0.816	(0.731,0.910)
AUC(0-6) (µg*hr/mL)	12	47.38(27.7)	45.51	51.74(32.8)	48.74	0.934	(0.848,1.028)
15 minutes (N=28)							
AUC(0-2) (µg*hr/mL)	12	16.67(26.4)	16.08	15.46(29.4)	14.75	1.090	(1.013,1.174)
AUC(2-4) (µg*hr/mL)	12	14.55(24.5)	14.09	16.22(27.3)	15.56	0.906	(0.847,96.8)
AUC(4-6) (µg*hr/mL)	12	13.35(26.5)	12.87	16.34(27.2)	15.69	0.820	(0.775,0.868)
AUC(0-6) (µg*hr/mL)	12	44.58(25.2)	43.11	48.01(27.4)	46.06	0.936	(0.881,0.995)
30 minutes (N=6)							
AUC(0-2) (µg*hr/mL)	8	16.55(33.2)	15.81	16.46(37.9)	15.48	1.021	(0.905,1.152)
AUC(2-4) (µg*hr/mL)	8	14.98(31.7)	14.39	18.18(31.7)	17.44	0.825	(0.728,0.934)
AUC(4-6) (µg*hr/mL)	8	12.87(30.0)	12.39	17.51(36.3)	16.54	0.749	(0.681,0.824)
AUC(0-6) (µg*hr/mL)	8	44.40(31.3)	42.65	52.15(34.8)	49.53	0.861	(0.786,0.944)
15 minutes (N=12)							
AUC(0-2) (µg*hr/mL)	8	16.97(25.8)	16.49	16.09(25.8)	15.63	1.055	(0.968,1.149)
AUC(2-4) (µg*hr/mL)	8	14.29(25.0)	13.85	16.96(23.4)	16.54	0.838	(0.766,0.915)
AUC(4-6) (µg*hr/mL)	8	13.19(24.4)	12.80	16.77(23.8)	16.32	0.784	(0.704,0.873)
AUC(0-6) (µg*hr/mL)	8	44.45(24.3)	43.21	49.81(24.0)	48.54	0.890	(0.819,0.967)

*The yellow highlighted numbers indicate 90% CI that extend outside of the 80%-125% no effect boundaries.
(source: IND 073686-0067, 1-6-3-partial-auc-summ.pdf, page 7/7)*

The pAUC analyses demonstrated several epochs which strayed outside the no-effect boundaries. For patients receiving oral CBZ q12 that switched to 30-minute infusions, pAUC₄₋₆ fell below the 80% no-effect boundary. For patients receiving oral CBZ q8h that switched to 30-minute infusions, the pAUC₂₋₄, pAUC₄₋₆, and pAUC₀₋₆ all fell below the 80% no-effect boundary. For patients receiving oral CBZ q12h that switched to 15-minute infusions, pAUC₄₋₆ hour fell below 80% no-effect boundary. Finally, for patients receiving oral CBZ q8h that switched to 15-minute infusions, the pAUC₂₋₄ and pAUC₄₋₆ fell below the no-effect boundaries. Sponsor stated that the pAUC deviations from the no-effect boundaries are not expected to be clinically significant. Sponsor indicated that a review of reported AEs and seizure frequencies in study OV-1015 did not identify any clinically relevant safety issues for patients who transition from oral q8h or oral q12h CBZ to IV q6h CBZ.

On 10/29/2013, the Agency issued a letter to the Sponsor with the following comments regarding the pAUC analyses:

- The shape of the concentration time curve of the API may be a determinant of the therapeutic effect
- Concentration time curves of all oral – IV paradigms show markedly dissimilar concentration time curves
- There is departure from the accepted bioequivalence standard at the 4 to 6 hour time point for the Q12 hour dosing regimen

- There is departure at three time intervals, i.e., 2 to 4 hour, 4 to 6 hour, and 0 to 6 hour in the Q8 hours dosing regimen after IV CBZ is delivered over 30 minutes, and at two time intervals, i.e., 2 to 4 hour and 4 to 6 hour after IV CBZ is delivered over 15 minutes
- We do not agree that these findings are clinically insignificant nor that such deviations could be managed in an ad hoc manner in a hospital setting
- You may propose a single, non-steady state, bioequivalence dose comparison that takes into consideration the issue of auto-induction
- You may be able to conduct simulations to investigate whether using alternative infusion regimens may result in better concordance between the steady state concentration-time profiles before versus after switching from oral to intravenous administration. Investigating different combinations of treatment parameters (e.g., infusion duration, proportion of daily oral dose to be administered intravenously, infusion interval duration, use of a loading dose, etc.) via pharmacokinetic simulations may identify an intravenous treatment regimen that more closely approximates the oral pharmacokinetics.
- At the present time we do not believe your data and its analysis are sufficiently complete for filing an NDA application

On 11/08/2013, the Sponsor provided responses to the Agency's 10/29/2014 communication. The following is a summary of the Sponsor's key points in their 11/08/2014 communication (IND 073686-0069):

- Sponsor believes deviations from pAUC were not accompanied by clinically important differences in AEs or seizure rate. Safety and efficacy data from the safety trial (13181A) were consistent with trial 13101 and were supportive of the proposed regimen.
- Conducting an additional trial wouldn't be helpful
- Based on analyses conducted using PK data from the NINDS study, Sponsor selected the 70% oral-to-IV conversion factor
- Proposal for PK simulations: 1) assess 75% dose, 2) assess 80% dose, 3) assess q4 dosing interval, 4) conduct literature search on effects of switching CBZ regimen on CBZ exposure, 5) change sample size.
- Sponsor proposed to submit the PK simulation results towards the end of January (after filing).

On 12/03/2013, the Agency responded to the Sponsor's 11/08/2013 communication. The following is a summary of the key points:

- Sponsor was informed that all data must be submitted with the NDA at the time of its submission
- Sponsor must respond to all issues raised at the 09/10/2013 pre-NDA meeting as well as issues raised in the 10/29/2013 written communication.

Sponsor filed NDA 206030 on 12/23/2013. The 12/23/2013 OV-1015-MODSIM report contained PK simulations which assessed the effect of various infusion regimens on pAUC BA analyses. Sponsor separated the group that received the oral CBZ q8h from the patients that received oral CBZ q12h for BA analyses. The following table summarizes the pAUC BA analyses for IV infusions administered *q6h* at oral –to-IV conversions of 70%, 75%, and 80%.

Table 18: BA Results Based on Simulated PK for IV q6h infusions When Administered as a 30-minute infusion (Top Panel) or 15-minute Infusion (Bottom Panel) to patients who Switched From oral CBZ q8h (Left Side) or oral CBZ q12h (Right Side) for a 70%, 75%, and 80% Conversion Factor

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR. 30-Minute IV Infusion Q 6 hr (N = 6)									Oral Dose = Q 12 hr ER. 30-Minute IV Infusion Q 6 hr (N = 17)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U
	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U
0 - 2 hr	102.1	90.5	115.2	109.4	97.0	123.5	116.7	103.4	131.7	108.7	99.9	118.3	116.5	107.1	126.8	124.3	114.2	135.3
2 - 4 hr	82.5	72.8	93.4	88.4	78.0	100.1	94.3	83.3	106.8	90.8	81.7	100.9	97.3	87.5	108.1	103.7	93.3	115.3
4 - 6 hr	74.9	68.1	82.4	80.2	72.9	88.3	85.6	77.6	94.1	81.6	73.1	91.0	87.4	78.4	97.5	93.2	83.6	104.0
6 - 8 hr	102.8	87.6	120.6	110.1	93.9	129.2	117.5	100.2	137.8	104.7	95.1	115.2	112.2	101.9	123.4	119.6	108.7	131.7
8 - 10 hr	93.0	83.2	103.8	99.6	89.2	111.2	106.2	95.1	118.7	95.2	86.6	104.7	102.4	92.8	112.1	108.8	98.9	119.6
10 - 12 hr	71.0	61.6	81.9	76.1	66.0	87.8	81.2	70.4	93.6	88.9	80.5	98.2	95.3	86.3	105.2	101.6	92.0	112.3
12 - 14 hr	95.6	85.5	106.7	102.4	91.7	114.4	109.2	97.8	122.0	108.7	99.9	118.3	116.5	107.1	126.8	124.3	114.2	135.3
14 - 16 hr	93.6	82.7	105.8	100.2	88.6	113.4	106.9	94.5	120.9	90.8	81.7	100.9	97.3	87.5	108.1	103.7	93.3	115.3
16 - 18 hr	80.0	71.5	89.6	85.7	76.6	96.0	91.5	81.7	102.4	81.6	73.1	91.0	87.4	78.4	97.5	93.2	83.6	104.0
18 - 20 hr	90.6	80.5	102.1	97.1	86.2	109.4	103.6	91.9	116.7	104.7	95.1	115.2	112.2	101.9	123.4	119.6	108.7	131.7
20 - 22 hr	87.0	79.0	95.7	93.2	84.7	102.6	99.4	90.3	109.4	95.2	86.6	104.7	102.0	92.8	112.1	108.8	98.9	119.6
22 - 24 hr	80.5	70.4	92.2	86.3	75.4	98.8	92.1	80.4	105.3	88.9	80.5	98.2	95.3	86.3	105.2	101.6	92.0	112.3

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR. 15-Minute IV Infusion Q 6 hr (N = 12)									Oral Dose = Q 12 hr ER. 15-Minute IV Infusion Q 6 hr (N = 28)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U
	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U	PE	90%CI	L 90%CI U
0 - 2 hr	105.5	96.8	114.9	113.0	103.7	123.1	120.5	110.6	131.3	109.0	101.3	117.4	116.8	108.5	125.8	124.6	115.8	134.1
2 - 4 hr	83.8	76.6	91.5	89.7	82.1	98.1	95.7	87.6	104.6	90.6	84.7	96.8	97.0	90.7	103.8	103.5	96.8	110.7
4 - 6 hr	78.4	70.4	87.3	84.0	75.5	93.6	89.6	80.5	99.8	82.0	77.5	86.8	87.9	83.1	93.0	93.8	88.6	99.2
6 - 8 hr	108.1	99.1	118.0	115.8	106.1	126.4	123.6	113.2	134.9	105.9	99.5	112.6	113.4	106.6	120.6	121.0	113.7	128.7
8 - 10 hr	88.6	80.2	97.8	94.9	86.0	104.8	101.3	91.7	111.8	96.3	91.8	101.0	103.2	98.4	108.3	110.1	105.0	115.5
10 - 12 hr	77.4	71.0	84.4	82.9	76.1	90.4	88.5	81.1	96.5	93.5	89.1	98.1	100.2	95.5	105.1	106.8	101.8	112.1
12 - 14 hr	101.0	92.9	109.8	108.2	99.6	117.6	115.4	106.2	125.5	109.0	101.3	117.4	116.8	108.5	125.8	124.6	115.8	134.1
14 - 16 hr	90.8	82.6	99.9	97.3	88.5	107.1	103.8	94.4	114.2	90.6	84.7	96.8	97.0	90.7	103.8	103.5	96.8	110.7
16 - 18 hr	81.9	73.9	90.7	87.7	79.2	97.2	93.6	84.5	103.7	82.0	77.5	86.8	87.9	83.1	93.0	93.8	88.6	99.2
18 - 20 hr	99.7	92.5	107.5	106.8	99.1	115.2	113.9	105.7	122.8	105.9	99.5	112.6	113.4	106.6	120.6	121.0	113.7	128.7
20 - 22 hr	84.9	77.1	93.3	90.9	82.7	100.0	97.0	88.2	106.7	96.3	91.8	101.0	103.2	98.4	108.3	110.1	105.0	115.5
22 - 24 hr	84.0	75.7	93.2	90.0	81.1	99.8	96.0	86.5	106.5	93.5	89.1	98.1	100.2	95.5	105.1	106.8	101.8	112.1

The yellow highlighted numbers indicate 90% CI that extend outside of the 80%-125% no effect boundaries.
(Source: ov-1015-modsim-report-v2.pdf, page 21/112)

The following table summarizes the pAUC BA analyses for IV infusions administered *q4h* for 70% dose *only* (for additional PK simulations using q4h infusions at 75%-80% dose, see the following table).

Table 19: BA Results Based on Simulated PK for IV q4h infusions When Administered as a 15-minute infusion (Top Panel) or 30-minute Infusion (Bottom Panel) to patients who Switched From oral CBZ q8h (Left Side) or oral CBZ q12h (Right Side) for a 70% conversion factor.

Dosing Interval Group	Infusion Length	Parameter	Oral to IV Conversion Factor	Geometric Least Square Mean				Ratio of Geometric Least Square Means IV/Oral	90% Confidence Interval for Ratio IV/Oral
				n	Oral	n	IV		
12	30 min	AUC(0-2)	70 %	17	15.6	17	16.0	102.7	94.5 - 111.7
12	30 min	AUC(2-4)	70 %	17	16.5	17	14.3	86.5	78.3 - 95.5
12	30 min	AUC(0-4)	70 %	17	32.1	17	30.3	94.3	86.2 - 103.2
12	30 min	AUC(4-6)	70 %	17	16.6	17	16.0	96.8	87.7 - 106.8
12	30 min	AUC(6-8)	70 %	17	16.2	17	14.3	88.0	79.9 - 97.1
12	30 min	AUC(8-10)	70 %	17	15.7	17	16.0	101.8	93.3 - 111.1
12	30 min	AUC(10-12)	70 %	17	15.2	17	14.3	93.9	85.4 - 103.2
12	30 min	AUC(12-14)	70 %	17	15.6	17	16.0	102.7	94.5 - 111.7
12	30 min	AUC(14-16)	70 %	17	16.5	17	14.3	86.5	78.3 - 95.5
12	30 min	AUC(16-18)	70 %	17	16.6	17	16.0	96.8	87.7 - 106.8
12	30 min	AUC(18-20)	70 %	17	16.2	17	14.3	88.0	79.9 - 97.1
12	30 min	AUC(20-22)	70 %	17	15.7	17	16.0	101.8	93.3 - 111.1
12	30 min	AUC(22-24)	70 %	17	15.2	17	14.3	93.9	85.4 - 103.2
8	30 min	AUC(0-2)	70 %	6	15.5	6	15.0	97.0	87.4 - 107.5
8	30 min	AUC(2-4)	70 %	6	17.4	6	13.2	75.9	66.8 - 86.3
8	30 min	AUC(0-4)	70 %	6	33.0	6	28.3	85.7	77.9 - 94.4
8	30 min	AUC(4-6)	70 %	6	16.5	6	15.0	90.7	82.8 - 99.4
8	30 min	AUC(6-8)	70 %	6	15.4	6	13.2	86.1	76.1 - 97.4
8	30 min	AUC(8-10)	70 %	6	15.5	6	15.0	97.0	87.4 - 107.5
8	30 min	AUC(10-12)	70 %	6	17.4	6	13.2	75.9	66.8 - 86.3
8	30 min	AUC(12-14)	70 %	6	16.5	6	15.0	90.7	82.8 - 99.4
8	30 min	AUC(14-16)	70 %	6	15.4	6	13.2	86.1	76.1 - 97.4
8	30 min	AUC(16-18)	70 %	6	15.5	6	15.0	97.0	87.4 - 107.5
8	30 min	AUC(18-20)	70 %	6	17.4	6	13.2	75.9	66.8 - 86.3
8	30 min	AUC(20-22)	70 %	6	16.5	6	15.0	90.7	82.8 - 99.4
8	30 min	AUC(22-24)	70 %	6	15.4	6	13.2	86.1	76.1 - 97.4
8	30 min	AUC(0-8)	70 %	6	65.0	6	56.5	87.0	79.3 - 95.5
8	30 min	AUC(0-16)	70 %	6	129.9	6	113.1	87.0	79.3 - 95.5
8	30 min	AUC(0-24)	70 %	6	194.9	6	169.6	87.0	79.3 - 95.5
12	15 min	AUC(0-2)	70 %	28	14.7	28	15.4	104.5	97.4 - 112.1
12	15 min	AUC(2-4)	70 %	28	15.6	28	13.6	87.1	81.2 - 93.5
12	15 min	AUC(0-4)	70 %	28	30.3	28	29.0	95.5	89.3 - 102.2
12	15 min	AUC(4-6)	70 %	28	15.7	28	15.4	98.2	92.3 - 104.5
12	15 min	AUC(6-8)	70 %	28	15.2	28	13.6	89.3	84.6 - 94.2
12	15 min	AUC(8-10)	70 %	28	14.6	28	15.4	105.3	99.5 - 111.6
12	15 min	AUC(10-12)	70 %	28	13.8	28	13.6	98.5	93.8 - 103.4
12	15 min	AUC(12-14)	70 %	28	14.7	28	15.4	104.5	97.4 - 112.1
12	15 min	AUC(14-16)	70 %	28	15.6	28	13.6	87.1	81.2 - 93.5
12	15 min	AUC(16-18)	70 %	28	15.7	28	15.4	98.2	92.3 - 104.5
12	15 min	AUC(18-20)	70 %	28	15.2	28	13.6	89.3	84.6 - 94.2
12	15 min	AUC(20-22)	70 %	28	14.6	28	15.4	105.3	99.5 - 111.6
12	15 min	AUC(22-24)	70 %	28	13.8	28	13.6	98.5	93.8 - 103.4
8	15 min	AUC(0-2)	70 %	12	15.6	12	15.3	97.8	90.0 - 106.3
8	15 min	AUC(2-4)	70 %	12	16.5	12	13.2	79.9	74.0 - 86.3
8	15 min	AUC(0-4)	70 %	12	32.2	12	28.5	88.6	82.0 - 95.7
8	15 min	AUC(4-6)	70 %	12	16.3	12	15.3	93.7	86.5 - 101.5
8	15 min	AUC(6-8)	70 %	12	15.2	12	13.2	86.7	79.3 - 94.7
8	15 min	AUC(8-10)	70 %	12	15.6	12	15.3	97.8	90.0 - 106.3
8	15 min	AUC(10-12)	70 %	12	16.5	12	13.2	79.9	74.0 - 86.3
8	15 min	AUC(12-14)	70 %	12	16.3	12	15.3	93.7	86.5 - 101.5
8	15 min	AUC(14-16)	70 %	12	15.2	12	13.2	86.7	79.3 - 94.7
8	15 min	AUC(16-18)	70 %	12	15.6	12	15.3	97.8	90.0 - 106.3
8	15 min	AUC(18-20)	70 %	12	16.5	12	13.2	79.9	74.0 - 86.3
8	15 min	AUC(20-22)	70 %	12	16.3	12	15.3	93.7	86.5 - 101.5
8	15 min	AUC(22-24)	70 %	12	15.2	12	13.2	86.7	79.3 - 94.7
8	15 min	AUC(0-8)	70 %	12	63.8	12	57.0	89.4	82.7 - 96.6
8	15 min	AUC(0-16)	70 %	12	127.6	12	114.1	89.4	82.7 - 96.6
8	15 min	AUC(0-24)	70 %	12	191.4	12	171.1	89.4	82.7 - 96.6

*The yellow highlighted numbers indicate 90% CI that extend outside of the 80%-125% no effect boundaries.
(Source: ov-1015-modsim-report.pdf, page 64/78)*

The filing communication letter (issued on 03/07/2014) indicated that the submission was sufficiently complete to permit a substantive review. However, the Sponsor was notified that the PK simulations provided in the original submission (12/27/2013) resulted in numerous pAUC epochs which fell outside of the 80-125% no-effect boundaries, particularly for the patients receiving oral CBZ q8h (see the previous table in this review). The Agency requested Sponsor conduct new simulations to explore the feasibility of utilizing different dosing regimen and/or infusion parameters. Sponsor was also advised to include $C_{\max}$ and $C_{\min}$ in the analyses and to stratify statistical analyses by dosing interval (e.g. "IR" q8h and "ER" q12). If the PK analyses of an alternate regimen resulted in epochs that were not entirely contained within the 80-125% no-effect boundaries, and Sponsor believed the regimen would not result in a clinically significant worsening of efficacy or safety, then Sponsor was advised to provide justification.

Sponsor provided a submission on 04/22/2014 (NDA 206030-0007) in response to the filing letter communication. The Sponsor provided results for the following *new* simulations in the OV-1015-MODSIM version 2:

- Assessed IV conversion factor of 75% of the total daily oral dose with a Q 4hr dosing interval and an infusion of 15 minutes or 30 minutes.
- Assessed IV conversion factor of 80% of the total daily oral dose with a Q 4hr dosing interval and an infusion of 15 minutes or 30 minutes.
- PK parameter modeling ($C_{\min}$ and $C_{\max}$) for IV Q4hr dosing interval for 15 minutes or 30 minutes when IV conversion factors are 70%, 75%, or 80%.
- PK parameter modeling ($C_{\min}$ and $C_{\max}$) for IV Q6hr dosing interval for 15 minutes or 30 minutes when IV conversion factors are 70%, 75%, or 80%.
- Bioequivalence assessment of pAUC and PK parameters for the above new alternative infusion regimens.
- Bioequivalence assessment of pAUC and PK parameters for those previously investigated Q6h IV dosing interval with 70%, 75% or 80% conversion factors and Q4h IV dosing interval with 70% conversion factor at infusion rate of 15 minutes or 30 minutes.

The following table contains the results of the Sponsor's statistical PK analyses based on PK simulations provided in OV-1015-MODSIM version 2.0 report.

Table 20: Results of BA Analyses Comparing IV/Oral PK utilizing C_{max} , C_{avg} , C_{min} , and AUC_{0-24hr} estimated based on PK Simulations in patients who were previously taking Q8h (IR) Oral CBZ (Left) and Q12h (XR) Oral CBZ (Right) and Switched to IV CBZ Infused over 30 Minutes (top), or 15 Minutes (bottom), Q6h, for 70%, 75%, or 80% Oral-to-IV Conversion

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI_L*	90%CI_U*	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
IR Q 8 hr (N =6)	30 min Infusion Q 6 hr	70%	99.0	87.7	111.8	87.5	79.6	96.3	83.0	72.8	94.7	87.5	79.6	96.3
IR Q 8 hr (N = 6)	30 min Infusion Q 6 hr	75%	106.0	93.9	119.7	93.8	85.2	103.2	88.9	78.0	101.5	93.8	85.2	103.2
IR Q 8 hr (N = 6)	30 min Infusion Q 6 hr	80%	113.1	100.2	127.7	100.1	90.9	110.1	94.9	83.2	108.2	100.1	90.9	110.1
ER Q 12 hr (N = 17)	30 min Infusion Q 6 hr	70%	113.0	101.4	126.1	94.8	86.3	104.2	91.5	83.3	100.5	94.8	86.3	104.2
ER Q 12 hr N = 17)	30 min Infusion Q 6 hr	75%	121.1	108.6	135.1	101.6	92.5	111.6	98.0	89.3	107.6	101.6	92.5	111.6
ER Q 12 hr (N = 17)	30 min Infusion Q 6 hr	80%	129.2	115.8	144.1	108.4	98.6	119.1	104.6	95.2	114.8	108.4	98.6	119.1

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI_L*	90%CI_U*	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
IR Q 8 hr (N =12)	15 min Infusion Q 6 hr	70%	129.4	117.6	142.4	90.3	83.1	98.2	79.8	72.8	87.4	90.3	83.1	98.2
IR Q 8 hr (N = 12)	15 min Infusion Q 6 hr	75%	138.6	126.0	152.6	96.8	89.0	105.2	85.5	78.0	93.6	96.8	89.0	105.2
IR Q 8 hr (N = 12)	15 min Infusion Q 6 hr	80%	147.9	134.4	162.8	103.2	94.9	112.2	91.2	83.2	99.9	103.2	94.9	112.2
ER Q 12 hr (N = 28)	15 min Infusion Q 6 hr	70%	126.5	112.8	141.8	96.0	91.0	101.4	94.7	89.8	99.9	96.0	91.0	101.4
ER Q 12 hr N = 28)	15 min Infusion Q 6 hr	75%	135.5	120.9	152.0	102.9	97.5	108.6	101.5	96.2	107.1	102.9	97.5	108.6
ER Q 12 hr (N = 28)	15 min Infusion Q 6 hr	80%	144.6	128.9	162.1	109.8	104	115.8	108.2	102.6	114.2	109.8	104	115.8

The yellow highlighted numbers indicate 90% CI that extend outside of the 80%-125% no effect boundaries
(source: ov-1015-modsim-report-v2.pdf, page 19/112)

Table 21: Results of BA Analyses Comparing IV/Oral PK utilizing C_{max}, C_{avg}, C_{min}, and AUC_{0-24hr} estimated based on PK Simulations in patients who were previously taking Q8h (IR) Oral CBZ (Left) and Q12h (XR) Oral CBZ (Right) and Switched to IV CBZ Infused over 30-minutes (top) or 15-minutes (bottom), Q4h, for 70%, 75%, or 80% Oral-to-IV Conversion

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI_L*	90%CI_U*	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
IR Q 8 hr (N =6)	30 min Infusion Q 4 hr	70%	89.6	81.5	98.4	87.0	79.3	95.5	91.1	82.6	100.6	87.0	79.3	95.5
IR Q 8 hr (N = 6)	30 min Infusion Q 4 hr	75%	95.7	87.4	105.4	93.2	84.9	102.3	97.7	88.5	107.8	93.2	84.9	102.3
IR Q 8 hr (N = 6)	30 min Infusion Q 4 hr	80%	102.3	93.2	112.4	99.5	90.6	109.2	104.2	94.4	115.0	99.5	90.6	109.2
ER Q 12 hr (N = 17)	30 min Infusion Q 4 hr	70%	98.5	89.9	108.0	94.7	86.6	103.7	99.9	91.5	109.2	94.7	86.6	103.7
ER Q 12 hr N = 17)	30 min Infusion Q 4 hr	75%	105.6	96.3	115.7	101.5	92.7	111.1	107.1	98.0	117	101.5	92.7	111.1
ER Q 12 hr (N = 17)	30 min Infusion Q 4 hr	80%	112.6	102.8	123.4	108.3	98.9	118.5	114.2	104.5	124.8	108.3	98.9	118.5

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI_L*	90%CI_U*	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
IR Q 8 hr (N =12)	15 min Infusion Q 4 hr	70%	108.8	100.2	118.0	89.4	82.7	96.6	90.5	83.5	98.1	89.4	82.7	96.6
IR Q 8 hr (N = 12)	15 min Infusion Q 4 hr	75%	116.5	107.4	126.4	95.8	88.6	103.5	97.0	89.4	105.1	95.8	88.6	103.5
IR Q 8 hr (N = 12)	15 min Infusion Q 4 hr	80%	124.3	114.6	134.9	102.2	94.5	110.4	103.4	95.4	112.2	102.2	94.5	110.4
ER Q 12 hr (N = 28)	15 min Infusion Q 4 hr	70%	111.8	101.6	123.0	96.9	91.5	102.5	104.4	99.0	110.2	96.5	91.5	102.5
ER Q 12 hr N = 28)	15 min Infusion Q 4 hr	75%	119.7	108.8	131.7	103.8	98.1	109.8	111.9	106.0	118.1	103.8	98.1	109.8
ER Q 12 hr (N = 28)	15 min Infusion Q 4 hr	80%	127.7	116.1	140.5	110.7	104.6	117.1	119.4	113.1	126.0	110.7	104.6	117.1

(source: ov-1015-modsim-report-v2.pdf, page 30/112)

Table 22: Results of BA Analyses Comparing IV/Oral PK Based on Simulated PK for IV q4h infusions When Administered as a 15-minute infusion (Top Panel) or 30-minute Infusion (Bottom Panel) to patients who Switched From oral CBZ q8h (Left Side) or oral CBZ q12h (Right Side)

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR. 15-Minute IV Infusion Q 4 hr (N = 12)									Oral Dose = Q 12 hr ER. 15-Minute IV Infusion Q 4 hr (N = 28)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
0 - 2 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	104.5	97.4	112.1	112.0	104.4	120.2	119.5	111.3	128.2
2 - 4 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	87.1	81.2	93.5	93.4	86.9	100.2	99.6	92.7	106.9
4 - 6 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	98.2	92.3	104.5	105.2	98.9	112.0	112.3	105.5	119.5
6 - 8 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	89.3	84.6	94.2	95.6	90.6	101.0	102.0	96.6	107.7
8 - 10 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	105.3	99.5	111.6	112.9	106.6	119.5	120.4	113.7	127.5
10 - 12 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	98.5	93.8	103.4	105.5	100.5	110.8	112.5	107.2	118.2
12 - 14 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	104.5	97.4	112.1	112.0	104.4	120.2	119.5	111.3	128.2
14 - 16 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	87.1	81.2	93.5	93.4	86.9	100.2	99.6	92.7	106.9
16 - 18 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	98.2	92.3	104.5	105.2	98.9	112.0	112.3	105.5	119.5
18 - 20 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	89.3	84.6	94.2	95.6	90.6	101.0	102.0	96.6	107.7
20 - 22 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	105.3	99.5	111.6	112.9	106.6	119.5	120.4	113.7	127.5
22 - 24 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	98.5	93.8	103.2	105.5	100.5	110.8	112.5	107.2	118.2

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR. 30-Minute IV Infusion Q 4 hr (N = 6)									Oral Dose = Q 12 hr ER. 30-Minute IV Infusion Q 4 hr (N = 17)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U	PE	90%CI_L	90%CI_U
0 - 2 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	102.7	94.5	111.7	110.1	101.2	119.7	117.4	108.0	127.7
2 - 4 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	86.5	78.3	95.5	92.6	83.9	102.3	98.8	89.5	109.1
4 - 6 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	96.8	87.7	106.8	103.7	93.9	114.4	110.6	100.2	122.1
6 - 8 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	88.0	79.9	97.1	94.3	85.6	104.0	100.6	91.3	110.9
8 - 10 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	101.8	93.3	111.1	109.1	100.0	119.1	116.4	106.4	127.0
10 - 12 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	93.9	85.4	103.2	100.6	91.5	110.6	107.3	97.6	118.0
12 - 14 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	102.7	94.5	111.7	110.1	101.2	119.7	117.4	108.0	127.7
14 - 16 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	86.5	78.3	95.5	92.6	83.9	102.3	98.8	89.5	109.1
16 - 18 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	96.8	87.7	106.8	103.7	93.9	114.4	110.6	100.2	122.1
18 - 20 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	88.0	79.9	97.1	94.3	85.6	104.0	100.6	91.3	110.9
20 - 22 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	101.8	93.3	111.1	109.1	100.0	119.1	116.4	106.7	127.0
22 - 24 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	93.9	85.4	103.2	100.6	91.5	110.6	107.3	97.6	118.0

(Source: ov-1015-modsim-report-v2.pdf, page 32/112)

Sponsor concluded that *the following infusion regimens* were not likely to result in clinically significant worsening of safety or efficacy and thus were acceptable:

- q4h IV interval, 75% conversion factor, 15-minute infusion (see tables 16 and 17)
- q4h IV interval, 75% conversion factor, 30-minute infusion (see tables 16 and 17)
- q6h IV interval, 75% conversion factor, 15-minute infusion (see tables 13 and 15)

Reviewer Analyses: The PK results from study OV-1015 demonstrate comparable exposures between IV and oral CBZ for the 30-minute IV infusion (see the Figure 3 in section 2.2.3).

However, despite the comparable C_{max} , C_{min} , and AUC_{0-24} associated with the 30-minute infusion, the steady-state IV PK profile drops below the corresponding oral PK profile from about 1 hour to 6 hours after administration (see Figure 4 in section 2.2.3).

Based on literature searches and internal discussions, this reviewer concluded that there is no established information regarding the exposure-efficacy relationship for the CBZ anticonvulsant effect. Overall, the available literature did not provide adequate exposure-response characterization in order to confidently interpret the clinical significance of the observed concentration drop in the figure above. The reviewer's analyses focused on assessing the significance of this concentration drop. However, the first step in the analyses was to address the proposed infusion durations of (b) (4) 30 minutes.

Infusion Duration Selection: The Sponsor provided PK and safety data for infusion durations that were 30-minutes, 15-minutes, and 2-5 minutes in duration. (b) (4)

(b) (4) e 15-minute infusion duration was associated with a greater AE frequency of in multiple AE categories compared to the 30-minute infusion (see the table below).

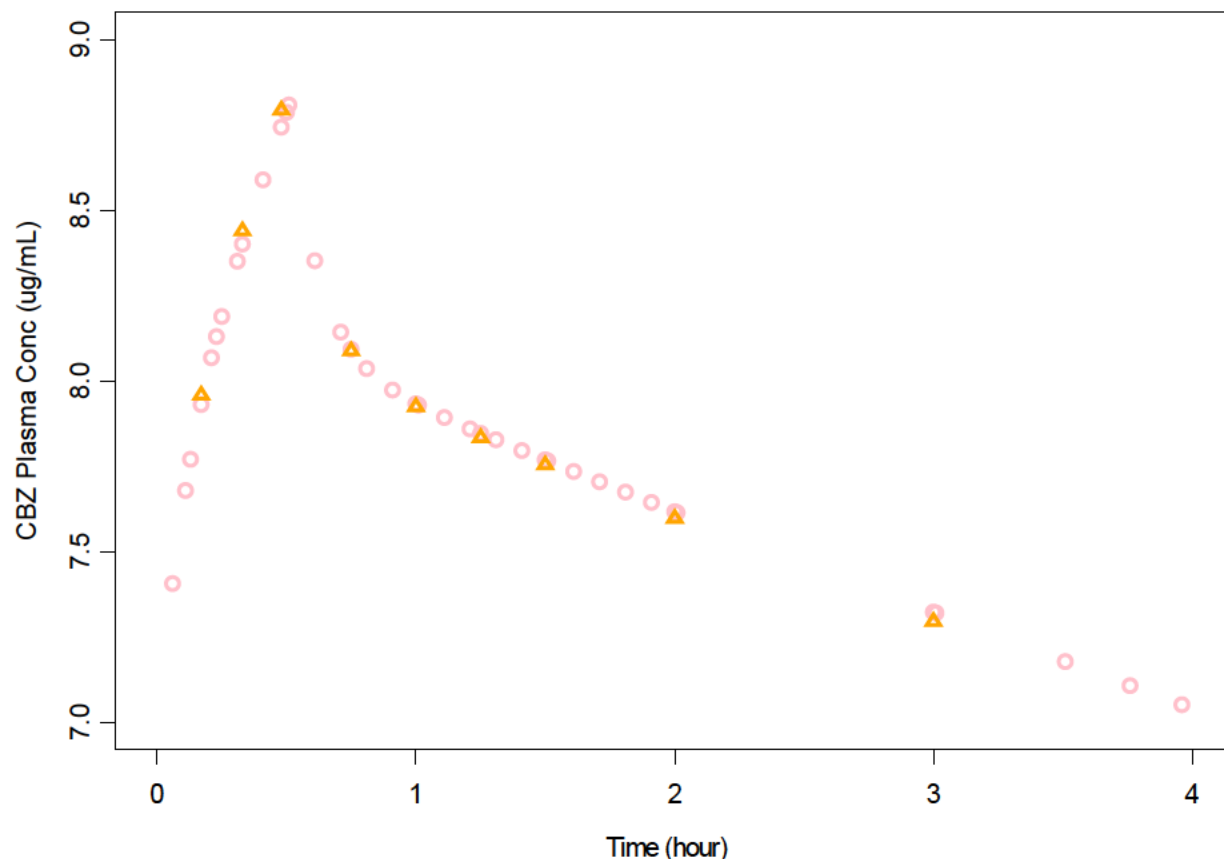
Table 23: Summary of Most Frequently Reported Adverse Events from Day 1 to Day 7 (Safety Population) in Study OV-1015

System Organ Class Preferred Term	Number of subjects (%)		
	15-minute Infusions (N=55)	30-minute Infusions (N=43)	Total (N=98)
General disorders and administration site conditions			
Infusion site reaction	3 (5.5)	1 (2.3)	4 (4.1)
Infections and infestations			
Cellulitis	4 (7.3)	2 (4.7)	6 (6.1)
Nervous system disorders			
Dizziness	8 (14.5)	4 (9.3)	12 (12.2)
Headache	3 (5.5)	1 (2.3)	4 (4.1)
Somnolence	3 (5.5)	2 (4.7)	5 (5.1)
Skin and subcutaneous tissue disorders			
Ecchymosis	3 (5.5)	1 (2.3)	4 (4.1)
Rash	4 (7.3)	0	4 (4.1)

(Ov-1015-study-report-body.pdf, pg 107/6880)

PK simulation was applied in order to assess the effect of infusion duration on CBZ exposures. The figure below demonstrates that the Reviewer was able to replicate the Sponsor's pharmacokinetic simulations.

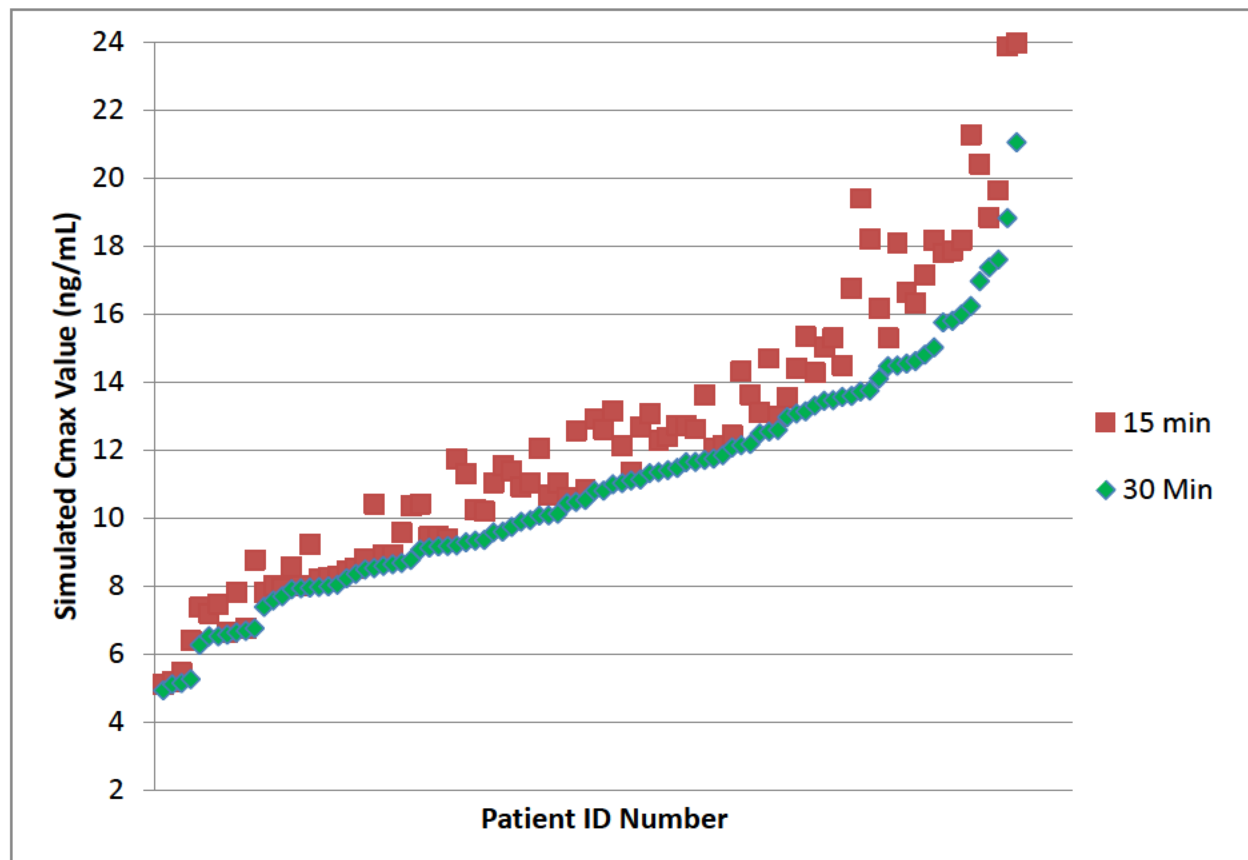
Figure 12: Sponsor's (Triangles) and Reviewer's (Circles) Simulated PK Profile For a Single Subjects After a 30-minute IV Infusion after 7 days of IV infusions q4h at a 70% oral-to-IV Conversion



The PK profile is a simulated PK profile of subject 103 after receiving 7 days of IV CBZ q4h, 30-minute infusions, 70% oral-to-IV conversion. Pink circles are data simulated by the FDA reviewer, orange triangles are data simulated by the Sponsor (from cbzsim70q4day1-7.xls, submitted in NDA 206030-0007).

Based on the concordance between Sponsor's simulations and FDA's simulations demonstrated in the figure above, the reviewer proceeded to utilize the same PK simulation method to assess the effects of infusion duration on IV CBZ PK. Simulated C_{max} and C_{min} values resulting from a 30-minute infusion (70% oral-to-IV conversion, q6h) were compared to a 15-minute Infusion. Consistent with what the Sponsor concluded in report 15926a (see section 4.2.4), the reviewer's PK simulations indicate that the 30-minute infusion is associated with a lower C_{max} than the 15-minute infusion (see the figure below).

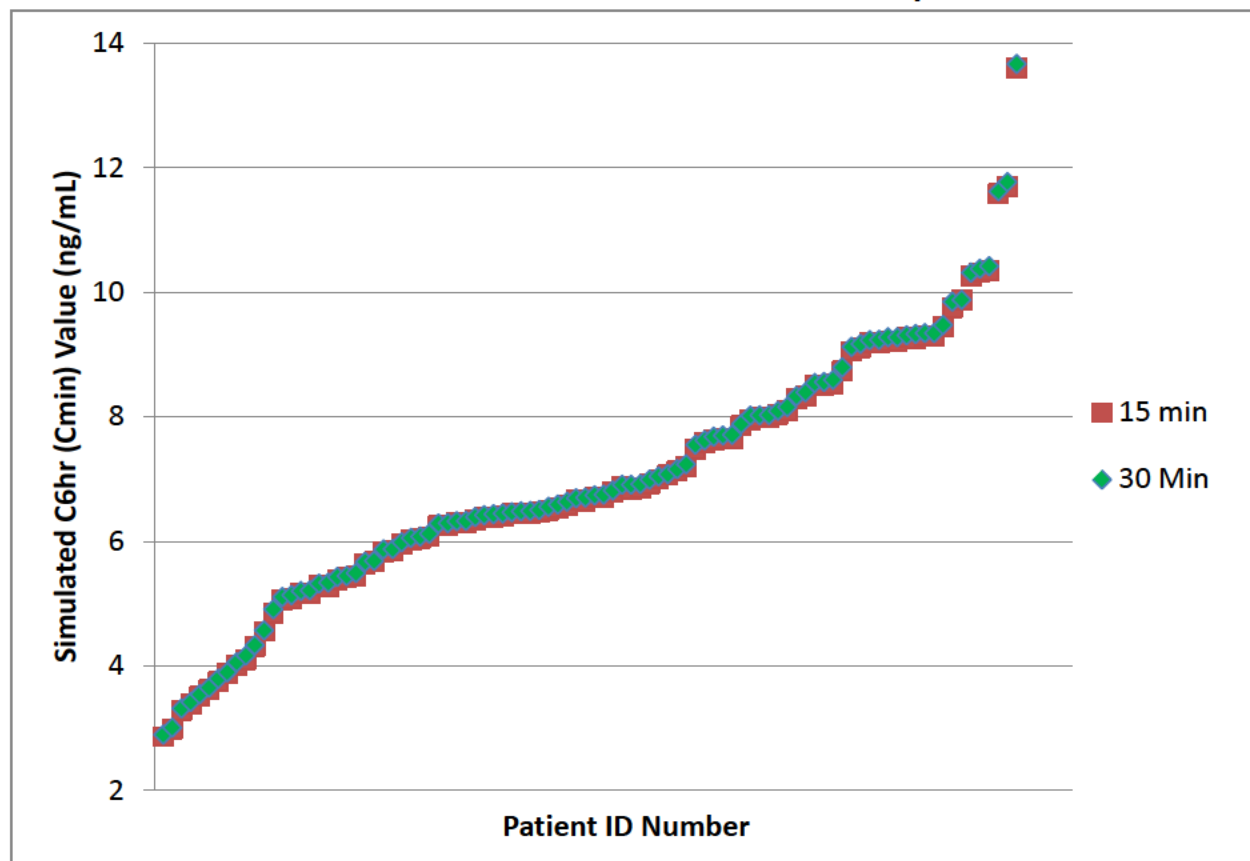
Figure 13: Simulated C_{max} after a 30-minute IV infusion and a 15-minute IV infusion both administered at 70% oral to IV conversion q6h



At each horizontal position on plot, the two points represents the simulated C_{max} when using a 15 minute infusion (red square) and simulated C_{max} when using a 30 minute infusion (green diamond) for the same patient.

The figure below demonstrates that IV C_{min} Day 7 for the 30 minute duration is comparable to the 15-minute duration.

Figure 14: Simulated C_{min} ($C_{6\text{hours}}$) after a 30-minute IV infusion and a 15-minute IV infusion at both administered at 70% oral to IV conversion q6h

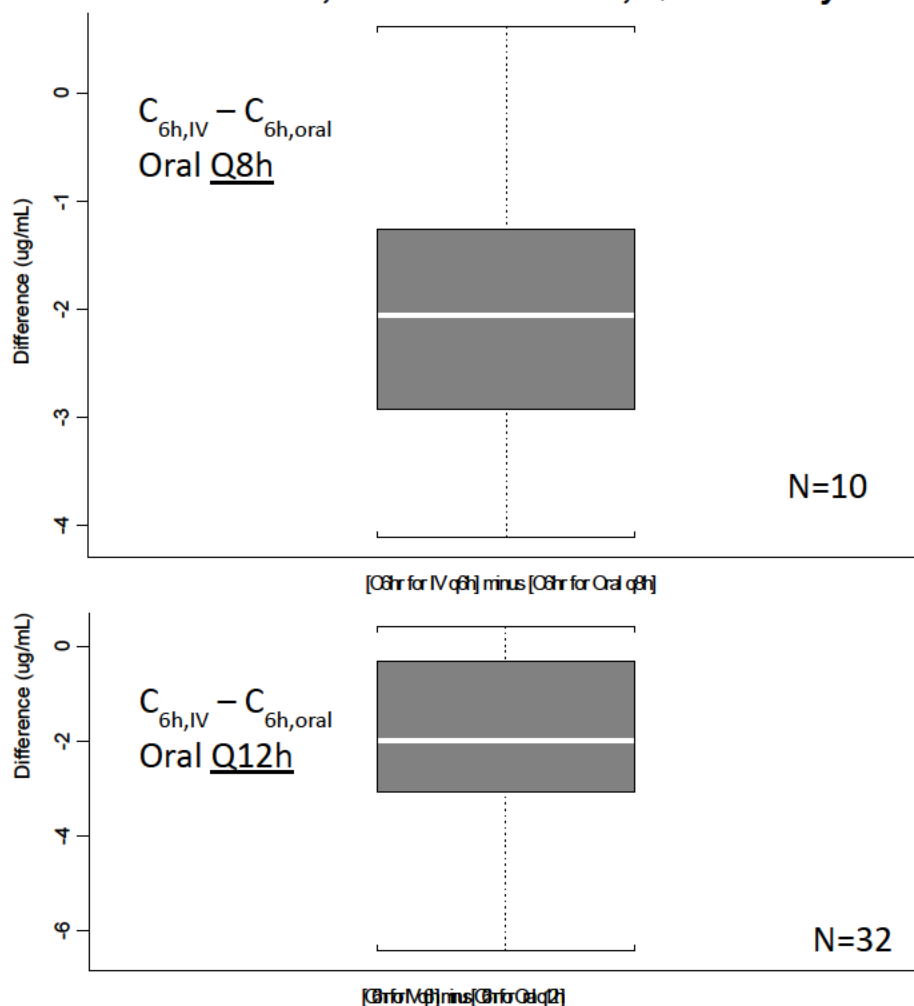


Since the 30-minute infusion duration has a lower frequency for various adverse events, produces a lower C_{max} , and a comparable C_{min} , the **30-minute infusion duration is the recommended infusion duration.**

As the 30-minute infusion is the recommended infusion, subsequent comparisons of observed PK will focus on patients who received 30-minute infusions in study OV-1015 (the patients who received 15-minute infusions were excluded).

“Worst-Case Scenario” Decrease in CBZ Exposure (C_{6h} , Day 7). Since the exposures achieved by IV CBZ infusions tended to decrease day-to-day throughout the 7-day infusion regimen applied in study OV-1015, the C_{6h} value after 7-days of IV infusions was considered as the “worst-case” scenario. In other words, C_{6h} values after 7 days of IV infusion are expected to be the lowest exposures achieved during the entire IV treatment period. For this reason, the C_{6h} values after 7 days of IV infusion were compared to the oral C_{6h} that patients were accustomed to from their established steady-state oral CBZ therapy. The figure below shows a boxplot of the range of intrasubject differences between IV C_{6h} on Day 7 and Oral C_{6h} on Day 0.

Figure 15: Boxplot Of the Intrasubject Difference of Oral C_{6h} on Day 0 and IV C_{6h} on Day 7 For Patients Receiving Oral Q8h (Top Panel) and Oral Q12h (Bottom Panel) CBZ that Switched to 70% conversion, 30-Minute Infusion, Q6h in Study OV-1015



For Patients Receiving 30-minute infusions in Study OV-1015, Day 7 IV C_{6h} is 2 $\mu\text{g/mL}$ lower than their Day 0 Oral C_{6h} . In particular, the IV C_{6h} is about $2 \pm 2 \mu\text{g/mL}$ lower on average than oral C_{6h} when switching from Q8h oral. In addition, the IV C_{6h} is about $2 \pm 1.4 \mu\text{g/mL}$ lower on average than oral C_{6h} when switching from Q12h oral. This decrease in C_{6hr} was compared to intrasubject variability in CBZ oral PK.

The Sponsor collected 12 hours of dense oral PK samples on Day 0. For patients receiving oral q8h CBZ and patients receiving oral q12h CBZ, there is insufficient data to assess the intrasubject variability for oral C_{6h} . However, Sponsor collected PK samples of oral C_{min} values at -14 days, -1 days, and on Day 0, (just prior to 9 am oral dose administration). For these reasons, intra-subject oral PK variability was assessed in terms of C_{min} . Figure 5 in section 2.2.3 shows the range and median observed CBZ C_{min} values observed while patients were on steady-state oral CBZ.

Though patients were at steady-state for their oral CBZ medication the mean intrasubject C_{min} range over 2-week period was $1.7 \pm 0.8 \mu\text{g/mL}$. The concentration decrease due to the “worst-case scenario” (Day 7 IV C_{6h}) is comparable to the intrasubject variability in oral C_{min} for patients receiving oral Q12h and oral Q8h CBZ (2 ± 2 and $2 \pm 1.4 \mu\text{g/mL}$, respectively). In order to assess the “worst-case scenario” for q6h, the reviewer conducted PK simulations.

Since only $n=1$ patient received oral q6h CBZ, PK simulations were utilized using PK parameters from other patients enrolled in the trial. In particular, PK parameters for oral q8h CBZ were estimated for use in these simulations. The doses received by the oral q8h patients in study OV-1015 were utilized in the PK simulations of an oral q6h regimen. Patients receiving oral q12h (extended-release) CBZ were excluded from these analyses. The simulated oral q6h PK profile is shown in the Figure 6 in section 2.2.3.

The PK simulations demonstrate that the C_{6h} decrease when switching from oral to IV Q6h is $1.38 \pm 2.5 \mu\text{g/mL}$. This predicted C_{6h} decrease when switching from oral Q6h is comparable to change observed when switching from oral q12h, or oral q8h.

Overall, patients experienced intra-subject CBZ C_{min} fluctuations during oral CBZ treatment that were of a comparable magnitude to the Day 7 IV CBZ C_{6h} decrease. In addition, for total CBZ (CBZ+CBZ-E), the mean intrasubject oral C_{min} fluctuation ($2.01 \pm 0.98 \mu\text{g/mL}$) was of a comparable magnitude to the Day 7 IV total CBZ C_{6h} decrease ($2.34 \pm 2.5 \mu\text{g/mL}$ for q12h patients and $2.73 \pm 1.57 \mu\text{g/mL}$ for q8h patients, respectively).

Though the intrasubject variability in oral C_{6h} could not be estimated, it is assumed to be no less than the intrasubject variability in oral C_{min} . This reviewer acknowledges that a sample of 3 oral C_{min} values is not adequate to characterize the oral C_{min} distribution within a subject. However, considering that a trend of $1.7 \pm 0.8 \mu\text{g/mL}$ CBZ C_{min} fluctuation over a 2-week period was observed in a $n=42$ sample, it is reasonable to compare oral C_{min} fluctuation with IV C_{6h} decrease. As such, the “worst-case scenario” decrease in Day 7 IV C_{6h} compared to Day 0 oral C_{6h} is not expected to result in a clinically significant worsening of efficacy. Based on the PK simulation of oral q6h CBZ, it is acceptable to include patients receiving oral q6h into the Carbella label.

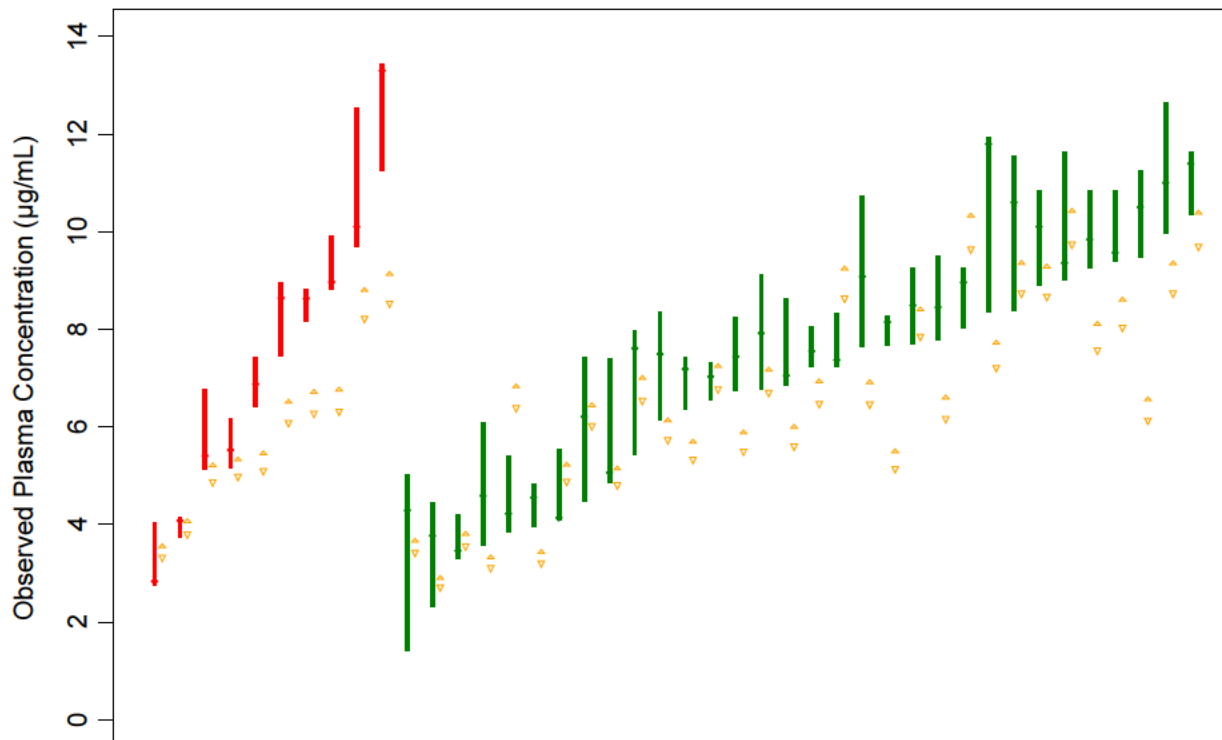
(b) (4)

Discussions with the medical officer have led to the understanding that administering Carbella more frequently (e.g. q4h instead of q6h) was not practical from a hospital logistics standpoint. For these reasons, the regimen that must be proposed for the label is 70% oral-to-IV conversion, 30-minute infusion, administered Q6h.

The additional simulations for the 75% oral-to-IV conversion and q4h administration interval are described in the sections below.

Oral-to-IV Conversion Selection: This reviewer conducted PK simulations to determine the effect of increasing the dose from 70% to 75% on the IV C_{min} after 7-days of IV infusions (q6h, 30-minute infusion). The observed oral C_{min} values are included in the plot to provide context of the IV C_{min} values (see the figure below).

Figure 16: Observed Intrasubject Oral Variability in C_{min} with Simulated Day 7 IV C_{min} after 7 days of 30 minute IV infusion, Q6h, for a 70% and 75% Oral-to-IV Conversion

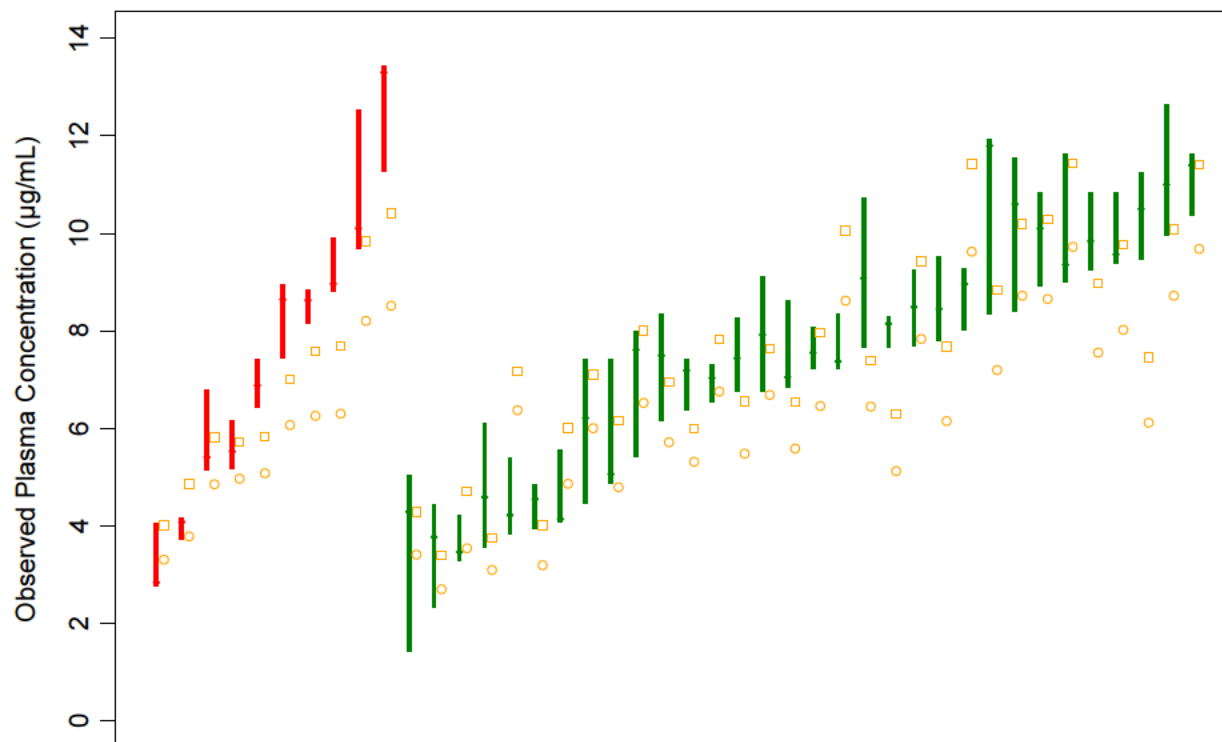


- Each line and overlapping diamond represents the range of observed oral C_{min} values for a single patient prior to 9 am oral dose on Days -14, -1, and 0.
- The observed oral C_{min} for patients that received oral CBZ q8h (n=10) is the red solid line and point (left side of plot). The observed oral C_{min} for patients that received oral CBZ q12h (n=32) is the green solid line and point (right side of plot). All observed patients received IV CBZ at 70% oral-to-IV conversion, q6h.
- The upward pointing orange triangle is the simulated IV C_{min} for a single patient after 7 days of IV CBZ at 75% dose, 30-minute infusion duration, Q6h.
- The downward pointing orange triangle is the simulated IV C_{min} for a single patient after 7 days of IV CBZ at 70% dose, 30-minute infusion duration, Q6h.

The mean C_{min} increase when switching from a 70% to 75% oral-to-IV conversion is 0.44 µg/mL (see the figure above). The reasons why the 70% oral-to-IV conversion was selected (rather than the 75% conversion) are described earlier in this section.

IV Dose Interval: This reviewer assessed the effect of Q4h interval for 30-minute infusions on IV C_{min} (IV C_{6h} for IV Q6h or IV C_{4h} for IV Q4h) after 7 days of IV infusion using pharmacokinetic simulations. The following plot provides a comparison of the C_{4h} values after 7 days of IV infusion Q4h as well as C_{6h} for IV infusion Q6h. The observed oral C_{min} range was overlaid in the plot below to provide context for the IV exposures achieved with Q4h and Q6h infusions.

Figure 17: Observed Intrasubject Variability in Oral C_{min} with Simulated C_{4h} after 7 days of IV infusion Q4h (squares) or C_{6h} after 7 days of IV infusion Q6h (circles), for a 70% Oral-to-IV Conversion, 30-Minute Infusion



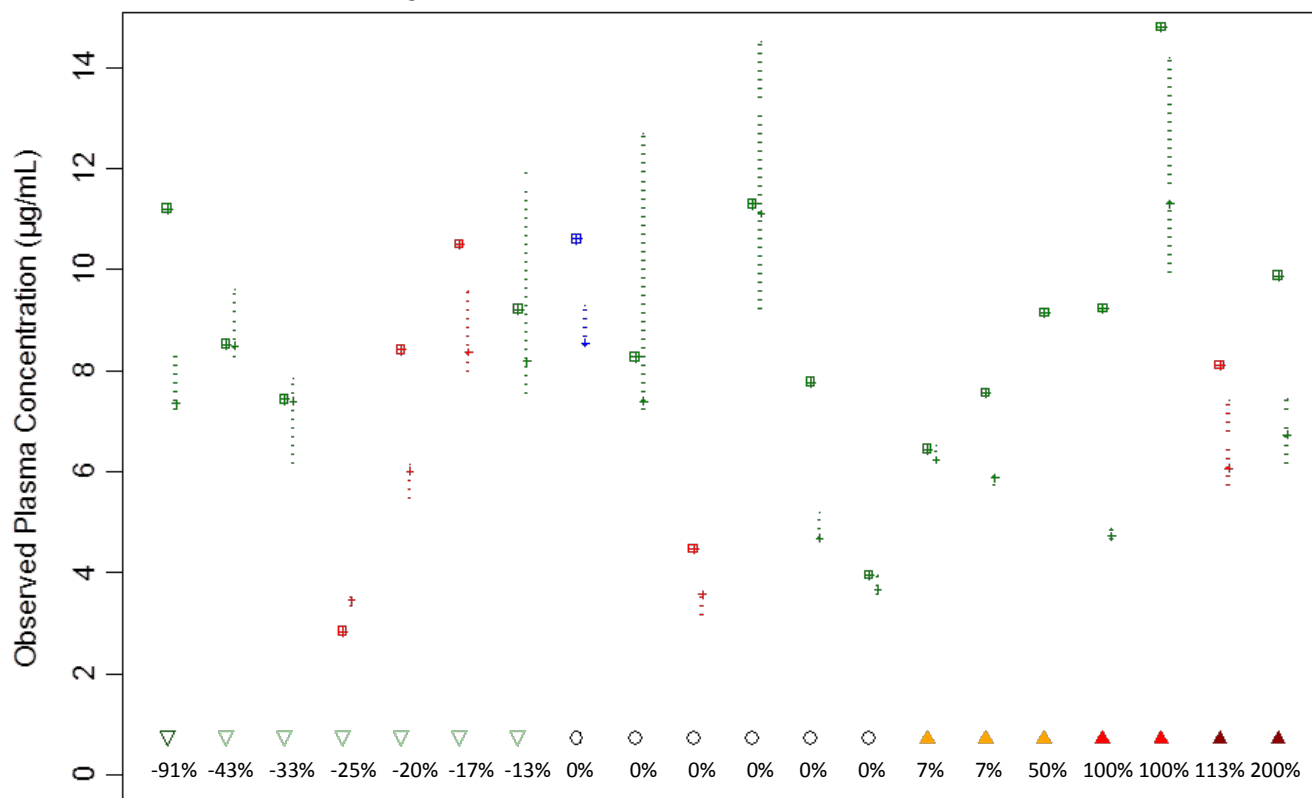
- Each line and overlapping diamond represents the range of observed oral C_{min} values for a single patient prior to 9am oral dose on Days -14, -1, and 0.
- The observed oral C_{min} for q8h ($n=10$) is the red solid line and overlapping diamond (left side of plot). The observed oral C_{min} for q12h ($n=32$) is the green solid line and overlapping diamond (right side of plot).
- The orange square is the simulated IV C_{4h} for a single patient after 7 days of IV CBZ at 70% dose, 30-minute infusion, Q4h.
- The orange circle is the simulated IV C_{6h} for a single patient after 7 days of IV CBZ at 70% dose, 30-minute infusion, Q6h.

The mean Increase in C_{4h} compared to C_{6h} when switching from IV Q4h to IV Q6h is 1.2 µg/mL (see the figure above). The reasons why the IV Q6h interval was selected (rather than the IV Q4h interval) are described earlier in this section.

Transition from IV CBZ to oral CBZ: The transition from IV CBZ to oral CBZ was not associated with an increased seizure risk. Table 5 (see section 2.2.3) demonstrates that the mean seizure frequency during the IV infusion as well as after IV infusion was lower than pre IV infusion in study OV-1015.

Table 6 (see section 2.2.3) demonstrates that seizure frequency increased during IV CBZ treatment (80% increase from baseline) then returned to a level that was 30% lower than baseline. The reason for the worsening of seizure frequency during IV treatment period is not clear. PK samples were not collected in study 13181a. Please see the clinical review by Dr. Steven Dinsmore for more information regarding seizure frequency observed during the trial. Though study OV-1015 was not designed to assess efficacy, seizure rate data is available for some patients in which PK data were collected. A graphical analysis was conducted to compare the change in seizure rate with change in CBZ C_{6h} when switching from oral to IV CBZ. The following plot compares the oral C_{6h} concentration on Day 0, the range of IV C_{6h} concentrations on Day 7, and the % change in seizure rate when switching from oral CBZ to IV CBZ.

Figure 18: Comparison of Percent Change from Baseline Seizure Rate, Oral C_{6h} on Day 0, and IV C_{min} Range (C_{6h} , C_{12h} , C_{18h}) on Day 7 in Patients Receiving Oral Q6h, Oral Q8h, and Oral Q12h CBZ that Switched to IV CBZ at a 70% conversion, 15-Minute or 30-Minute Infusion Duration, Q6h.



- Oral q6h (n=1) is Blue, Oral q8h (n=5) is Red, Oral q12h (n=14) is Green. 70% oral-to-IV conversion, 15-min and 30-min infusions, Study OV-1015A
- Dashed lines and +'s Represents the Range of Observed IV C_{min} (C_{6h} , C_{12h} , C_{18h}) on Day 7
- Squares Represent the observed oral C_{6h} on Day 0
- The % listed at the bottom of the plot is the % seizure rate change when transitioning from pre-IV therapy to during-IV therapy. The down triangle, circle, and up triangle represent a decrease, no change, and increase in seizure rate when switching to IV therapy.

Though the data are limited (n=20 subjects with both IV and oral PK and seizure rate data), the plot above suggests there is no clear relationship between change in C_{6h} and change from baseline seizure rate when switching from oral to IV CBZ.

Overall, the safety data suggest that the transitioning directly from IV CBZ to oral CBZ is acceptable.

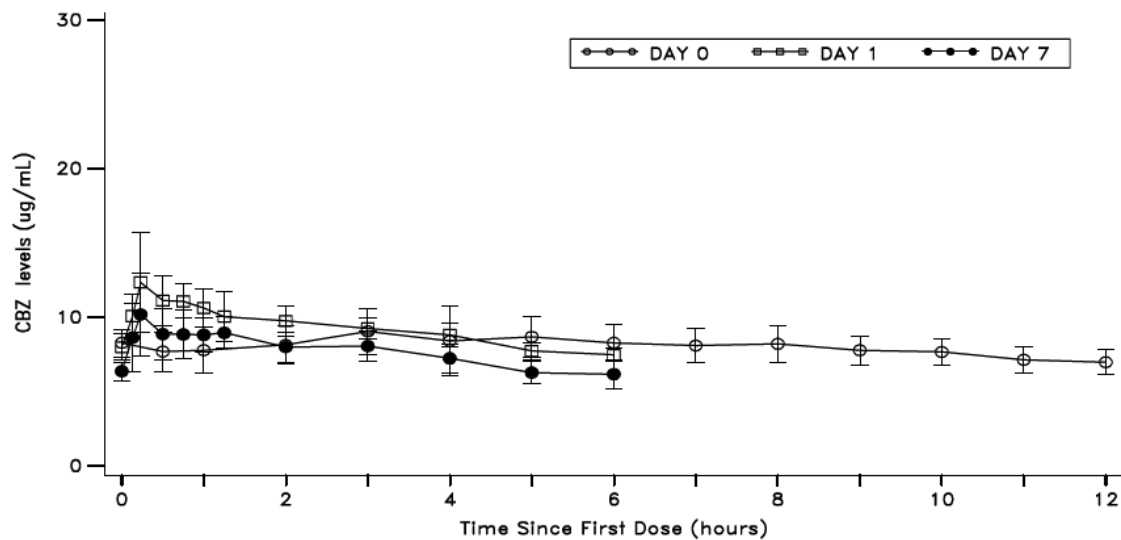
4.2 Individual Study Review

4.2.1 OV-1015: PK, Safety, and Tolerability of Carbella

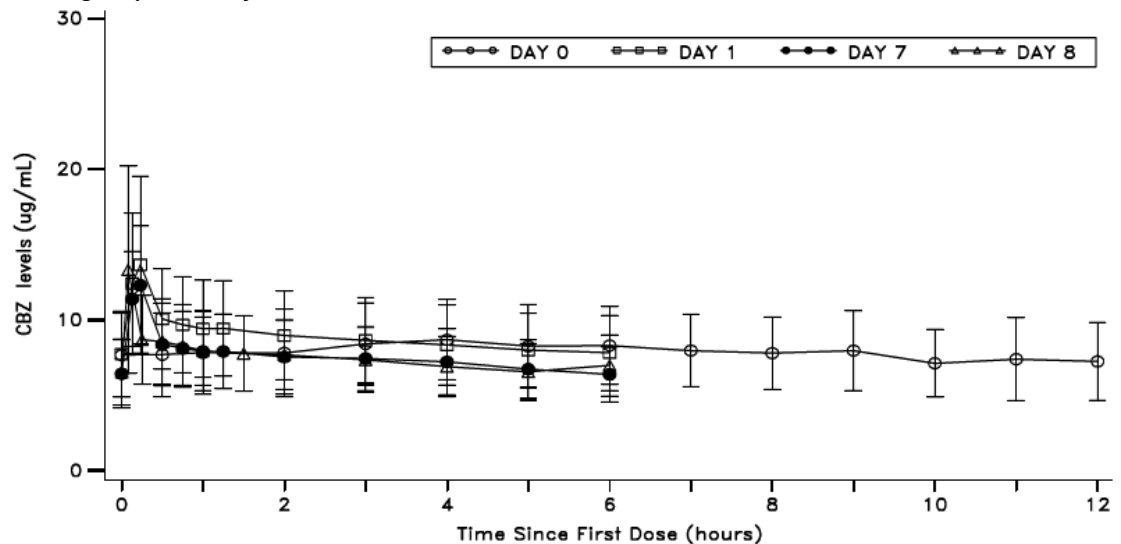
Study Report#	OV-1015																																																																																
Title	A Sequential, Open-Label Study of the Pharmacokinetics and Safety of Intravenous Carbamazepine Relative to Oral Carbamazepine in Adult Patients with Epilepsy																																																																																
Objectives	<u>Primary:</u> - Assess safety, tolerability and PK of IV CBZ as a 30- and 15-minute infusion relative to orally administered CBZ - Compare the steady-state PK of IV CBZ (Day 7) relative to oral CBZ (Day 0) <u>Secondary:</u> - To assess the safety, tolerability and PK of IV CBZ when administered over a 2-5-minute infusion in a subset of patients. - To assess the safety, tolerability and PK of IV CBZ in patients with mild or moderate renal impairment.																																																																																
Study Design	Phase 1, multi-center, sequential, open label study in n=98 epilepsy patients on oral CBZ (q6h, q8h, or q12h) who are switched to IV CBZ q6h for 7 days at a total daily dose of 70% of the oral daily dose. There were n=32, n=45, and n=1 patients that recieved 30 minute, 15-minute infusion, or 2-5 minute infusions that had evaluable PK. <table><tr><th colspan="5">Table 6. Summary of Subject Demographics (Safety Population)</th></tr><tr><th>Variable</th><th>2-5-minute Infusions¹</th><th>15-minute Infusions¹</th><th>30-minute Infusions</th><th>Total</th></tr><tr><td>Overall</td><td>N=12</td><td>N=55</td><td>N=43</td><td>N=98</td></tr><tr><td>Age</td><td></td><td></td><td></td><td></td></tr><tr><td>Mean (SD)</td><td>44.8 (10.3)</td><td>45.8 (11.6)</td><td>44.4 (11.9)</td><td>45.2 (11.7)</td></tr><tr><td>Range</td><td>23 - 60</td><td>23 - 68</td><td>20 - 68</td><td>20 - 68</td></tr><tr><td>Gender</td><td></td><td></td><td></td><td></td></tr><tr><td>Male, n (%)</td><td>6 (50.0)</td><td>26 (47.3)</td><td>16 (37.2)</td><td>42 (42.9)</td></tr><tr><td>Female, n (%)</td><td>6 (50.0)</td><td>29 (52.7)</td><td>27 (62.8)</td><td>56 (57.1)</td></tr><tr><td>Race</td><td></td><td></td><td></td><td></td></tr><tr><td>White or Caucasian, n (%)</td><td>11 (91.7)</td><td>50 (90.9)</td><td>34 (79.1)</td><td>84 (85.7)</td></tr><tr><td>Black or African American, n (%)</td><td>1 (8.3)</td><td>5 (9.1)</td><td>8 (18.6)</td><td>13 (13.3)</td></tr><tr><td>Asian, n (%)</td><td>0</td><td>0</td><td>1 (2.3)</td><td>1 (1.0)</td></tr><tr><td>Ethnicity</td><td></td><td></td><td></td><td></td></tr><tr><td>Hispanic or Latino, n (%)</td><td>0</td><td>3 (5.5)</td><td>2 (4.7)</td><td>5 (5.1)</td></tr><tr><td>Not Hispanic or Latino, n (%)</td><td>12 (100.0)</td><td>52 (94.5)</td><td>41 (95.3)</td><td>93 (94.9)</td></tr></table>	Table 6. Summary of Subject Demographics (Safety Population)					Variable	2-5-minute Infusions ¹	15-minute Infusions ¹	30-minute Infusions	Total	Overall	N=12	N=55	N=43	N=98	Age					Mean (SD)	44.8 (10.3)	45.8 (11.6)	44.4 (11.9)	45.2 (11.7)	Range	23 - 60	23 - 68	20 - 68	20 - 68	Gender					Male, n (%)	6 (50.0)	26 (47.3)	16 (37.2)	42 (42.9)	Female, n (%)	6 (50.0)	29 (52.7)	27 (62.8)	56 (57.1)	Race					White or Caucasian, n (%)	11 (91.7)	50 (90.9)	34 (79.1)	84 (85.7)	Black or African American, n (%)	1 (8.3)	5 (9.1)	8 (18.6)	13 (13.3)	Asian, n (%)	0	0	1 (2.3)	1 (1.0)	Ethnicity					Hispanic or Latino, n (%)	0	3 (5.5)	2 (4.7)	5 (5.1)	Not Hispanic or Latino, n (%)	12 (100.0)	52 (94.5)	41 (95.3)	93 (94.9)
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	Table 16. Summary of Exposure to IV CBZ and SBECD (Safety Population)						
	Infusion Time ²	CL _{cr} ² (mL/min)	IV CBZ (mg) ³		SBECD (mg) ⁵		
			Per Dose ⁴ Mean (SD) Range	Total Daily Dose Mean (SD) Range	Per Dose ⁴ Mean (SD) Range	Total Daily Dose Mean (SD) Range	
PK Assessment	30 minutes	Overall, n=43	163.7 (48.5)	654.8 (194.1)	4092.4 (1213.1)	16369.5 (4852.5)	
			88.0 - 262.3	351.8 - 1049.3	2198.8 - 6558.1	8795.0 - 26232.5	
		≥80, n=33	169.5 (49.7)	677.8 (198.8)	4236.3 (1242.5)	16945.3 (4970.0)	
			88.0 - 262.3	351.8 - 1049.3	2198.8 - 6558.1	8795.0 - 26232.5	
		50 – 80, n=9	142.6 (39.4)	570.3 (157.5)	3564.5 (984.1)	14258.0 (3936.3)	
			105.9 - 210.0	423.5 - 839.8	2646.9 - 5248.8	10587.5 - 20995.0	
	15 minutes	Overall, n=55	166.2 (75.9)	664.7 (303.5)	4154.1 (1897.1)	16616.3 (7588.3)	
			70.3 - 350.2	281.2 - 1400.7	1757.5 - 8754.4	7030.0 - 35017.5	
		≥80, n=49	164.7 (77.0)	658.8 (308.1)	4117.4 (1925.9)	16469.5 (7703.5)	
			70.3 - 350.2	281.2 - 1400.7	1757.5 - 8754.4	7030.0 - 35017.5	
		50 – 80, n=4	184.1 (66.3)	736.5 (265.2)	4603.3 (1657.7)	18413.3 (6630.8)	
			140.1 - 280.3	560.4 - 1121.2	3502.5 - 7007.5	14010.0 - 28030.0	
	2-5 minutes	≥80, n=12	179.5 (91.3)	718.0 (365.2)	4487.7 (2282.3)	17950.8 (9129.0)	
			70.3 - 350.2	281.2 - 1400.7	1757.5 - 8754.4	7030.0 - 35017.5	
	Statistical Analysis	Sponsor collected PK samples for CBZ as well as CBZ-epoxide according to the following schedule.					
		<u>30 Minute Infusions:</u>					
		<i>Day 1 and 7, first infusion:</i> -1, 10, 20, 29, 45, 60, 75, 90 minutes, 2, 3, 4, 5 hours after infusion start.					
		<i>Day 1 and 7, second, third, fourth infusion:</i> -1 and 29 minutes after infusion start					
		<i>Day 2 through Day 6:</i> 30 seconds prior to infusion start, 30 seconds prior to infusion completion.					
		<u>15 Minute Infusions:</u>					
<i>Day 1 and 7, first infusion:</i> -1, 7.5, 14, 30, 45, 60, 75 minutes, 2, 3, 4, and 5 hours after infusion start.							
<i>Day 1 and 7, second, third, fourth infusion:</i> -1 and 14 minutes after infusion start							
<i>Day 2 through Day 6:</i> 30 seconds prior to infusion start, 30 seconds prior to infusion completion.							
<u>5 Minute Infusions (Occurred on Day 8 only):</u>							
Bioanalytical Methods	<i>First infusion:</i> -30 seconds, 5, 15, 30, 45, 60, 90 minutes, 2, 3, 4, 5, and 6 hours after infusion start.						
	<i>Second, Third, and Fourth infusions:</i> 30 seconds prior to infusion, 30 second after infusion						
	<u>2 Minute Infusions (Occurred on Day 9 only):</u>						
	<i>First infusion:</i> -30 seconds, 2, 15, 30, 45, 60, 90 minutes, 2, 3, 4, 5, and 6 hours after infusion start.						
<i>Second, Third, and Fourth infusions:</i> 30 seconds prior to infusion start, 30 seconds prior to infusion completion.							
C _{min} , C _{max} , AUC ₀₋₂₄ were computed and summarized by arithmetic mean (%CV), geometric LS mean, by infusion duration (30-, 15-, and 2-5 mintues) and by route of administration (oral or IV) for CBZ, CBZ-epoxide, and “total CBZ” (CBZ+CBZ-epoxide). Sposnor computed the geometric mean ratio and its 90% confidence interval.							
HPLC-MS/MS Analyte: Carbamazepine Internal standard (IS): Carbamazepine-d10 Limit of quantitation: 0.05 µg/mL Average recovery of drug (%): 90.9 - 102 Average recovery of IS (%): 90.1							

	Standard curve concentration: 0.05, 0.1, 0.2, 0.8, 3, 12, 50 µg/mL Standards accuracy range (%): -3.84 to 6.22 Standards precision range (%): 3.94 to 6.71 QC range: 0.15, 0.4, 1.5, 6, 9, 37.5 µg/mL QC precision range (%): 2.58 to 9.48 QC accuracy range (%): -4.82 to 12.7% The assay is considered acceptable.																																																																																																																																			
Population/ Demographic s	N=98 epilepsy patients																																																																																																																																			
PK Results	PK Parameters and Bioavailability Assessments for CBZ In Patients with Normal Renal Function <table><tr><th rowspan="2">Infusion Time¹ Pharmacokinetic Parameter</th><th colspan="2">IV Infusion</th><th colspan="2">Oral</th><th rowspan="2">Ratio of Geometric LS Means²</th><th rowspan="2">90% CI for Ratio</th></tr><tr><th>Arithmetic Mean (%CV)</th><th>Geometric LS Mean</th><th>Arithmetic Mean (%CV)</th><th>Geometric LS Mean</th></tr><tr><td colspan="7">30 minutes (N=23)</td></tr><tr><td>AUC(0-24) (µg.hr/mL)</td><td>186.40 (28.04)</td><td>178.99</td><td>204.58 (33.19)</td><td>192.74</td><td>0.929</td><td>(0.864, 0.998)</td></tr><tr><td>Cmax (µg/mL)</td><td>10.76 (34.91)</td><td>10.15</td><td>9.81 (33.74)</td><td>9.24</td><td>1.099</td><td>(1.010, 1.197)</td></tr><tr><td>Cmin (µg/mL)</td><td>6.28 (27.15)</td><td>6.04</td><td>7.21 (34.26)</td><td>6.77</td><td>0.892</td><td>(0.828, 0.961)</td></tr><tr><td colspan="7">15 minutes (N=41)</td></tr><tr><td>AUC(0-24) (µg.hr/mL)</td><td>180.08 (25.02)</td><td>174.25</td><td>191.45 (26.00)</td><td>184.48</td><td>0.945</td><td>(0.905, 0.986)</td></tr><tr><td>Cmax (µg/mL)</td><td>11.77 (34.42)</td><td>11.14</td><td>9.05 (24.85)</td><td>8.75</td><td>1.273</td><td>(1.174, 1.381)</td></tr><tr><td>Cmin (µg/mL)</td><td>6.01 (26.68)</td><td>5.79</td><td>6.71 (28.38)</td><td>6.43</td><td>0.900</td><td>(0.857, 0.944)</td></tr><tr><td colspan="7">2-5 minutes (N=10)</td></tr><tr><td>AUC(0-24) (µg.hr/mL)</td><td>179.42 (28.34)</td><td>172.60</td><td>189.85 (32.64)</td><td>179.68</td><td>0.961</td><td>(0.887, 1.041)</td></tr><tr><td>Cmax (µg/mL)</td><td>13.44 (50.98)</td><td>12.09</td><td>8.97 (31.47)</td><td>8.52</td><td>1.419</td><td>(1.062, 1.896)</td></tr><tr><td>Cmin (µg/mL)</td><td>6.18 (33.19)</td><td>5.86</td><td>6.57 (34.62)</td><td>6.19</td><td>0.947</td><td>(0.865, 1.037)</td></tr></table> Mean ± SD CBZ PK Profile Following oral (Day 0) and <u>30-minute IV Infusions</u> (Day 1 through 7) in Subjects with Normal Renal Function. <table><caption>Approximate data points from the graph</caption><thead><tr><th>Time (hours)</th><th>DAY 0 (ug/mL)</th><th>DAY 1 (ug/mL)</th><th>DAY 7 (ug/mL)</th></tr></thead><tbody><tr><td>0</td><td>8.5</td><td>9.0</td><td>7.5</td></tr><tr><td>1</td><td>11.5</td><td>12.0</td><td>10.0</td></tr><tr><td>2</td><td>10.0</td><td>10.5</td><td>8.5</td></tr><tr><td>4</td><td>9.0</td><td>9.5</td><td>7.5</td></tr><tr><td>6</td><td>8.5</td><td>8.5</td><td>7.0</td></tr><tr><td>8</td><td>8.5</td><td>8.5</td><td>7.0</td></tr><tr><td>10</td><td>9.0</td><td>9.0</td><td>7.0</td></tr><tr><td>12</td><td>8.0</td><td>8.0</td><td>7.0</td></tr></tbody></table> Mean ± SD CBZ PK Profile Following oral (Day 0) and <u>15-minute IV Infusions</u> (Day 1 through 7) in Subjects with Normal Renal Function.	Infusion Time ¹ Pharmacokinetic Parameter	IV Infusion		Oral		Ratio of Geometric LS Means ²	90% CI for Ratio	Arithmetic Mean (%CV)	Geometric LS Mean	Arithmetic Mean (%CV)	Geometric LS Mean	30 minutes (N=23)							AUC(0-24) (µg.hr/mL)	186.40 (28.04)	178.99	204.58 (33.19)	192.74	0.929	(0.864, 0.998)	Cmax (µg/mL)	10.76 (34.91)	10.15	9.81 (33.74)	9.24	1.099	(1.010, 1.197)	Cmin (µg/mL)	6.28 (27.15)	6.04	7.21 (34.26)	6.77	0.892	(0.828, 0.961)	15 minutes (N=41)							AUC(0-24) (µg.hr/mL)	180.08 (25.02)	174.25	191.45 (26.00)	184.48	0.945	(0.905, 0.986)	Cmax (µg/mL)	11.77 (34.42)	11.14	9.05 (24.85)	8.75	1.273	(1.174, 1.381)	Cmin (µg/mL)	6.01 (26.68)	5.79	6.71 (28.38)	6.43	0.900	(0.857, 0.944)	2-5 minutes (N=10)							AUC(0-24) (µg.hr/mL)	179.42 (28.34)	172.60	189.85 (32.64)	179.68	0.961	(0.887, 1.041)	Cmax (µg/mL)	13.44 (50.98)	12.09	8.97 (31.47)	8.52	1.419	(1.062, 1.896)	Cmin (µg/mL)	6.18 (33.19)	5.86	6.57 (34.62)	6.19	0.947	(0.865, 1.037)	Time (hours)	DAY 0 (ug/mL)	DAY 1 (ug/mL)	DAY 7 (ug/mL)	0	8.5	9.0	7.5	1	11.5	12.0	10.0	2	10.0	10.5	8.5	4	9.0	9.5	7.5	6	8.5	8.5	7.0	8	8.5	8.5	7.0	10	9.0	9.0	7.0	12	8.0	8.0	7.0
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Mean ± SD CBZ PK Profile Following oral (Day 0) and 2-5 minute IV Infusions (Day 1 through 7) in Subjects with Normal Renal Function.



Steady State CBZ Pharmacokinetic Parameters For Oral Versus IV Routes, By Infusion Duration, and By Normal Renal Function Versus Mild Renal Impairment

Parameter Variable	Normal Renal Function ^a			Mild Renal Impairment ^a	
	2-5-minute Infusions ^c	15-minute Infusions ^c	30-minute Infusions	15-minute Infusions ^c	30-minute Infusions ^c
AUC(0-24) (µg·hr/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	189.85 (61.96)	191.45 (49.78)	204.58 (67.89)	193.41 (28.12)	177.02 (42.97)
%CV	32.64	26.00	33.19	14.54	24.27
Geometric mean	179.68	184.48	192.74	191.96	172.02
Median	195.99	193.72	207.76	185.85	189.07
Range	91.2 - 257.9	86.4 - 295.6	96.3 - 319.9	169.3 - 232.6	110.9 - 227.3
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	179.42 (50.85)	180.08 (45.05)	186.40 (52.27)	184.61 (24.87)	152.99 (34.33)
%CV	28.34	25.02	28.04	13.47	22.44
Geometric mean	172.60	174.25	178.99	183.41	149.18
Median	182.09	167.59	185.20	178.24	153.45
Range	105.3 - 248.2	81.1 - 279.6	88.2 - 273.6	162.7 - 219.3	98.8 - 190.6

Cmax (µg/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	8.97 (2.82)	9.05 (2.25)	9.81 (3.31)	9.35 (1.33)	8.49 (1.97)
%CV	31.47	24.85	33.74	14.19	23.26
Geometric mean	8.52	8.75	9.24	9.28	8.29
Median	9.35	9.05	9.82	8.93	8.38
Range	4.28 - 12.00	4.28 - 13.00	4.46 - 16.80	8.33 - 11.20	6.13 - 11.90
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	13.44 (6.85)	11.77 (4.05)	10.76 (3.76)	10.50 (2.40)	8.92 (1.93)
%CV	50.98	34.42	34.91	22.85	21.63
Geometric mean	12.09	11.14	10.15	10.29	8.74
Median	11.30	11.10	10.40	10.51	8.49
Range	4.72 - 27.50	4.79 - 23.80	4.53 - 20.20	8.09 - 12.90	6.47 - 12.00
Cmin (µg/mL)					
Oral CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	6.57 (2.28)	6.71 (1.91)	7.21 (2.47)	6.70 (1.02)	6.28 (1.76)
%CV	34.62	28.38	34.26	15.26	28.07
Geometric mean	6.19	6.43	6.77	6.64	6.05
Median	6.65	6.77	7.47	6.35	6.88
Range	3.06 - 9.89	2.90 - 11.60	3.16 - 11.90	5.89 - 8.19	3.65 - 8.52
IV CBZ	N=10	N=41	N=23	N=4	N=9
Mean (SD)	6.18 (2.05)	6.01 (1.60)	6.28 (1.70)	5.81 (0.75)	4.99 (1.27)
%CV	33.19	26.68	27.15	12.97	25.40
Geometric mean	5.86	5.79	6.04	5.77	4.84
Median	6.19	5.89	6.00	5.79	4.63
Range	3.75 - 9.22	2.57 - 9.38	3.17 - 9.11	4.94 - 6.71	3.17 - 6.37

(source: ov-1015-study-report-body.pdf, page 82/6880)

Table 19. Weekly Seizure Rates by Treatment Phase (Subjects with 30-Minute and 15-Minute Infusions)

Renal Function	Pre IV Day -28 to Day 0	IV Day 1 to Day 7	Post IV Day 8 to Day 38
Normal Renal Function¹			
30-minute infusion (n)	34	34	33
Mean (SD)	0.4 (1.1)	0.3 (0.6)	0.2 (0.4)
Range	0.0 - 5.8	0.0 - 2.0	0.0 - 1.4
15-minute infusion (n)	39	39	37
Mean (SD)	1.8 (6.3)	1.2 (2.9)	1.4 (4.5)
Range	0.0 - 34.1	0.0 - 16.0	0.0 - 24.3
Total (n)	73	73	70
Mean (SD)	1.1 (4.7)	0.8 (2.2)	0.8 (3.3)
Range	0.0 - 34.1	0.0 - 16.0	0.0 - 24.3
Mild Renal Impairment¹			
30-minute infusion (n)	9	9	8
Mean (SD)	3.0 (4.4)	0.9 (1.8)	2.2 (2.8)
Range	0.0 - 13.5	0.0 - 4.0	0.0 - 7.9
15-minute infusion (n)	4	4	4
Mean (SD)	0.2 (0.5)	0.5 (1.0)	0.1 (0.2)
Range	0.0 - 0.9	0.0 - 2.0	0.0 - 0.5
Total (n)	13	13	12
Mean (SD)	2.1 (3.8)	0.8 (1.5)	1.5 (2.5)
Range	0.0 - 13.5	0.0 - 4.0	0.0 - 7.9

(source: ov-1015-study-report-body.pdf, page 116/6880)

Safety

The majority of AEs were mild or moderate. One SAE was observed but was deemed not related to study drug. There three transient increases in hematology / chemistry: metamyelocytes, blood triglycerides, and alanine aminotransferase which were all considered “possibly related to study drug”. No clinically meaningful changes in urinary biomarkers of renal tubular integrity or glomerular filtration, or estimated CLcr. The route of administration (IV versus oral) does not appear to affect the CBZ-concentration / QTcF relationship.

	Comparison of QTcF Data for Oral CBZ Versus IV CBZ (source: ov-1015-study-report-body.pdf, page 136/6880)
Conclusions	In subjects with normal renal function, overall exposure and maximum and minimum plasma levels of plasma CBZ and total CBZ were bioequivalent between oral CBZ and IV CBZ administered over 30 minutes at 70% of the total daily oral dose.
Comment	<i>Sponsor's statistical PK analyses grouped all patients together (e.g. PK data from oral q8h and oral q12h were all included in the analyses). However, when bioequivalence assessments are conducted on the patients receiving oral CBZ q8h separately from the patients receiving oral CBZ q12h, BE fails for both dose groups (see Table 17 in section 4.1.2).</i> <i>Patients with receiving 30-minute infusions with mild RI did not appear to have an increase in seizure rate after switching to IV CBZ compared to oral CBZ use (though the sample size is limited, n=9). Similarly, patients with normal renal function did not appear to have an increase in seizure frequency during IV CBZ use compared to oral CBZ. This observation is supportive of the notion that patients with mild renal impairment do not require a CBZ dose adjustment when switching from oral to IV CBZ.</i>

4.2.2 15841a: Captisol Pharmacokinetics Supplemental Report (from Study OV-1015)

Study Report #	15841a																																																																											
Title	Captisol Pharmacokinetics Report: OV-1015																																																																											
Objectives	- To assess the PK of Captisol administered as an intravenous infusion following single (Day 1) and multiple dose administration (Days 7) of the IV CBZ/Captisol formulation, based on cohorts 2A (normal renal function; infusion rate = 0.5 hr), 2B (normal renal function; infusion rate = 0.25 hr), 3A (mild renal impairment; infusion rate = 0.5 hr) and 3B (mild renal impairment; infusion rate = 0.25 hr) as described in study OV-1015. - To examine the effect of mild renal impairment (Clcr = 50-80 mL/min) on the PK of IV Captisol so as to allow PK comparison of the above cohort 3A vs. 2A and cohort 3B vs. 2B of study OV-1015, respectively. - To compare the influence of infusion time (0.25 hr vs. 0.50 hr) on PK of Captisol to allow PK comparison of cohorts 2A vs. 2B and 3A vs. 3B of study OV-1015, respectively.																																																																											
Study Design	Study OV-1015 was a phase 1, multi-center, sequential, open label study in epilepsy patients on oral CBZ (q6h, q8h, or q12h) who are switched to IV CBZ q6h for 7 days at a total daily dose of 70% of the oral daily dose. Of the n=98 patients that were enrolled into study OV-1015, 35 subjects with normal renal function, 16 subjects with mild renal impairment, and 2 subjects with moderate renal impairment were included in the Captisol PK analyses described in report 15875a. Please refer to the Study synopsis for Study OV-1015 for additional details. Planned Cohort Assignments for Analyses Described in Report 15875a <table><thead><tr><th>Dosing Cohort</th><th>Minimum Number of Patients (N)^a</th><th>CL_{CR} (mL/min)</th><th>Oral CBZ Daily Dose (mg)</th><th>Infusion Time (min)</th></tr></thead><tbody><tr><td>1A</td><td>8</td><td>>80</td><td>400-800</td><td>30</td></tr><tr><td>1B</td><td>4</td><td>>80</td><td>400-800</td><td>15</td></tr><tr><td>1C^b</td><td>4</td><td>>80</td><td>400-800</td><td>15, then 2-5</td></tr><tr><td>2A</td><td>8</td><td>>80</td><td>>800-2000</td><td>30</td></tr><tr><td>2B</td><td>4</td><td>>80</td><td>>800-2000</td><td>15</td></tr><tr><td>2C^b</td><td>4</td><td>>80</td><td>>800-2000</td><td>15, then 2-5</td></tr><tr><td>3A₁</td><td>4</td><td>>50-80</td><td>400-800</td><td>30</td></tr><tr><td>3A₂</td><td>4</td><td>>50-80</td><td>>800-2000</td><td>30</td></tr><tr><td>3B</td><td>8</td><td>>50-80</td><td>400-2000</td><td>15</td></tr><tr><td>3C₁^b</td><td>4</td><td>>50-80</td><td>400-800</td><td>15, then 2-5</td></tr><tr><td>3C₂^b</td><td>4</td><td>>50-80</td><td>>800-2000</td><td>15, then 2-5</td></tr><tr><td>4A₁</td><td>4</td><td>≥30-50</td><td>400-800</td><td>30</td></tr><tr><td>4A₂</td><td>4</td><td>≥30-50</td><td>>800-2000</td><td>30</td></tr><tr><td>4B</td><td>4</td><td>≥30-50</td><td>400-2000</td><td>15</td></tr></tbody></table> CBZ = carbamazepine; CL_{CR} = creatinine clearance ^a The minimum number of patients needed to complete the study before allowing enrollment into subsequent dosing cohorts. ^b Patients in Dosing Cohorts 1C, 2C and 3C were treated the same as patients from Dosing Cohorts 1B, 2B and 3B, respectively, but consented to stay an additional day for CBZ infusions over 2 to 5 minutes.	Dosing Cohort	Minimum Number of Patients (N) ^a	CL _{CR} (mL/min)	Oral CBZ Daily Dose (mg)	Infusion Time (min)	1A	8	>80	400-800	30	1B	4	>80	400-800	15	1C ^b	4	>80	400-800	15, then 2-5	2A	8	>80	>800-2000	30	2B	4	>80	>800-2000	15	2C ^b	4	>80	>800-2000	15, then 2-5	3A ₁	4	>50-80	400-800	30	3A ₂	4	>50-80	>800-2000	30	3B	8	>50-80	400-2000	15	3C ₁ ^b	4	>50-80	400-800	15, then 2-5	3C ₂ ^b	4	>50-80	>800-2000	15, then 2-5	4A ₁	4	≥30-50	400-800	30	4A ₂	4	≥30-50	>800-2000	30	4B	4	≥30-50	400-2000	15
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PK Assessment	Please refer to the Study synopsis for Study OV-1015 for details on PK sampling.																																																																											
Statistical	Sponsor estimated AUC, AUC, AUC, CL, CL/kg, C _{avg} , C _{max} , T _{max} , C _{min} , λ _z , t _{1/2} ,																																																																											

Analysis	DFL (degree of fluctuation, $(C_{\max}-C_{\min})/C_{\text{avg}}$), MRT ($AUMC_{0-\infty} / AUC_{0-\infty}$), V_{ss} , V_{ss}/kg , V_z , V_z/kg , AUC_{0-t} accumulation ratio, $C_{\max}$ accumulation ratio. Some parameters were normalized to a 5000 mg dose (e.g. $C_{\max}/D$, C_{avg}/D , etc.).
Bioanalytical Methods	LC-MS/MS Analyte: Captisol Internal standard (IS) : Captisol-G Limit of quantitation: 5 µg/mL Average recovery of drug (%): 100.7% to 123.9% Average recovery of IS (%): 114% Standard curve concentration (ng/ml) : 5 to 200 Standards accuracy range (%): 96.7 – 104.5% Standards precision range (%): ≤ 14.5% QC range: 15, 75, 150 µg/mL QC accuracy range (%): 92.1 – 106.4% QC precision range (%): ≤ 14.5% The assay is considered acceptable.
Population/ Demographics	35 subjects with normal renal function, 16 subjects with mild renal impairment, and 2 subjects with moderate renal impairment who participated in study OV-1015 were included in the analyses described in study report 15875a

Results

Demographics In the Evaluable PK Population

Cohort	2A	2B	3A	3B	4A	4B	All
n	16	19	9	7	1	1	53
Age (years)	39.9 (10.9)	43.8 (10.2)	54 (4)	51.6 (8.6)	56 (0)	65 (0)	45.9 (11.3)
Weight (kg)	93.1 (18.7)	99.7 (26.6)	64.2 (4)	61.2 (8.6)	65.0 (0)	58.4 (0)	84.9 ()
CLcr (mL/min) screening	130.9 (24.3)	136.5 (28.4)	69.2 (7.2)	76.7 (8.0)	56 (0)	57 (0)	112.5 (37.4)
CLcr (L/hr/kg) study	0.0918 (0.0166)	0.0855 (0.0110)	0.0725 (0.0065)	0.0803 (0.0116)	0.0557 (0)	0.0632 (0)	0.0835 (0.0146)
Captisol Dose (mg / q6h)	5195 (694)	5734 (1421)	3840 (1067)	4750 (1947)	2625 (0)	4375 (0)	5035 (1419)
Captisol Dose (mg/kg/q6h)	58.1 (14.1)	61.6 (22.0)	59.9 (16.4)	77.1 (27.8)	40.4 (0)	75.0 (0)	62.2 (20.1)

Quantities are expressed as mean (standard deviation). (source: 15875a-report.pdf pg 13/116).

2A = Oral CBZ >800 to 2000 mg/day and CLcr ≥ 90 mL/min with infusions of IV CBZ of 30 minutes

2B = Oral CBZ >800 to 2000 mg/day and CLcr ≥ 90 mL/min with infusions of IV CBZ of 15 minutes

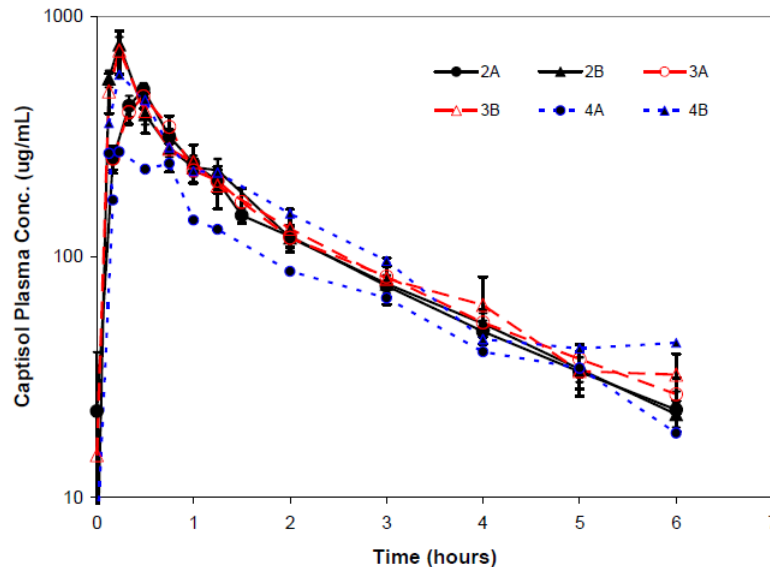
3A = Oral CBZ 400-2000 mg/day and CLcr 60-89 mL/min with infusions of IV CBZ of 30 minutes.

3B = Oral CBZ 400-2000 mg/day and CLcr 60-89 mL/min with infusions of IV CBZ of 15 minutes.

4A = Oral CBZ 400-2000 mg/day and CLcr 30-59 mL/min with infusions of IV CBZ of 30 minutes.

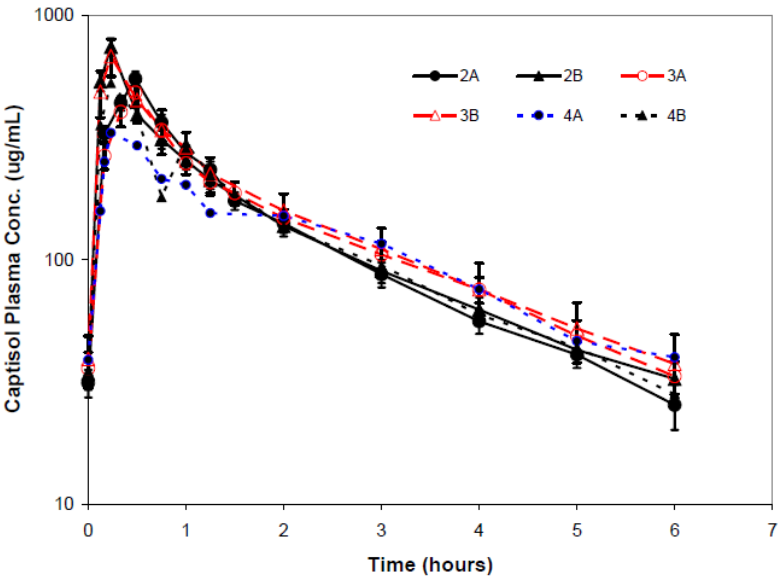
4B = Oral CBZ 400-2000 mg/day and CLcr 30-59 mL/min with infusions of IV CBZ of 15 minutes.

Mean (± SE) Captisol Plasma Concentrations After IV CBZ on Day 1



(source: 15841a-report.pdf pg 17/42)

Mean (± SE) Captisol Plasma Concentrations After IV CBZ on Day 7



(source: 15841a-report.pdf pg 18/42)

Single Dose (Day 1) Captisol IV PK in Subjects with Normal Renal Function, Mild and Moderate Renal Impairment

		Normal Renal Function				Mild Impairment				Moderate Impairment	
Infusion = 0.5 hr		Cohort = 2A				Cohort = 3A				Cohort = 4A	
		n	Mean	%CV	GeoMean	n	Mean	%CV	GeoMean	n	Mean
Dose	(mg)	15	5192	13.8	5145	9	3840	27.8	3705	1	2625
Dose	(mg/kg)	15	58.8	24.4	57.1	9	59.9	27.4	57.8	1	40.4
C _{max}	(ug/mL)	15	520	22.9	507	9	478	30.4	457	1	273
T _{max}	(hr)	15	0.443	15.5	0.438	9	0.496	21.6	0.487	1	0.483
AUC _{0-t}	(ug*hr/mL)	15	720	25.5	697	9	741	28.7	711	1	550
AUC _{0-∞}	(ug*hr/mL)	15	782	27.3	753	9	808	30.0	771	1	596
λ _z	(1/hr)	15	0.4783	20.7	0.4669	9	0.4370	19.9	0.4299	1	0.4060
t _{1/2}	(hr)	15	1.53	29.7	1.48	9	1.64	17.9	1.61	1	1.71
Cl	(L/hr)	15	6.96	20.3	6.84	9	4.89	21.0	4.80 b	1	4.41
CL/kg	(L/hr/kg)	15	0.0787	29.0	0.0759	9	0.0763	21.6	0.0749	1	0.0678
V _{ss}	(L)	15	12.1	27.7	11.8	9	9.38	12.6	9.31 b	1	9.08
V _{ss} /kg	(L/kg)	15	0.134	25.2	0.131	9	0.146	11.1	0.145	1	0.140
V _z	(L)	15	14.9	19.6	14.6	9	11.2	11.3	11.2 b	1	10.9
V _z /kg	(L/kg)	15	0.166	20.3	0.163	9	0.175	8.7	0.174	1	0.167
MRT	(hr)	15	1.82	41.0	1.72	9	1.98	20.4	1.94	1	2.06
Clcr	(L/hr)	15	8.35	20.3	8.20	9	4.66	11.4	4.63 b	1	3.62
Clcr/kg	(L/hr/kg)	15	0.0925	18.3	0.0911	9	0.0725	8.9	0.0722 b	1	0.0557
Infusion = 0.25 hr		Cohort = 2B				Cohort = 3B				Cohort = 4B	
		n	Mean	%CV	GeoMean	n	Mean	%CV	GeoMean	n	Mean
Dose	(mg)	19	5734	24.8	5570	7	4750	41.0	4339 b	1	4375
Dose	(mg/kg)	18	61.6	35.7	57.7	7	77.1	36.1	71.4	1	75.0
C _{max}	(ug/mL)	19	779	30.9	744 a	7	725	48.8	656	1	570
T _{max}	(hr)	19	0.228	10.9	0.226 a	7	0.218	18.8	0.213	1	0.233
AUC _{0-t}	(ug*hr/mL)	19	830	31.4	792	7	832	45.8	759	1	842
AUC _{0-∞}	(ug*hr/mL)	19	881	31.5	840	7	905	46.0	824	1	959
λ _z	(1/hr)	19	0.4729	12.7	0.4690	7	0.4394	20.9	0.4314	1	0.3762
t _{1/2}	(hr)	19	1.49	14.1	1.48	7	1.64	20.0	1.61	1	1.84
Cl	(L/hr)	19	6.78	22.2	6.63	7	5.30	12.9	5.27 b	1	4.56
CL/kg	(L/hr/kg)	18	0.0697	22.1	0.0681	7	0.0884	20.7	0.0867 b	1	0.07817
V _{ss}	(L)	19	11.6	29.7	11.1	7	10.3	33.2	9.79	1	11.0
V _{ss} /kg	(L/kg)	18	0.118	20.8	0.116	7	0.169	35.4	0.161 b	1	0.188
V _z	(L)	19	14.7	29.0	14.1	7	12.5	23.8	12.2	1	12.1
V _z /kg	(L/kg)	18	0.149	20.6	0.146	7	0.207	27.3	0.201 b	1	0.208
MRT	(hr)	19	1.71	20.1	1.68	7	1.94	29.8	1.86	1	2.40
Clcr	(L/hr)	19	8.30	21.6	8.13	4	4.87	11.9	4.83 b	1	3.69
Clcr/kg	(L/hr/kg)	18	0.0855	12.9	0.0848	4	0.0803	14.4	0.0796	1	0.0632

(source: 15841a-report.pdf pg 20/42)

Steady-State (Day 7) Captisol IV PK in Subjects with Normal Renal Function, Mild and Moderate Renal Impairment

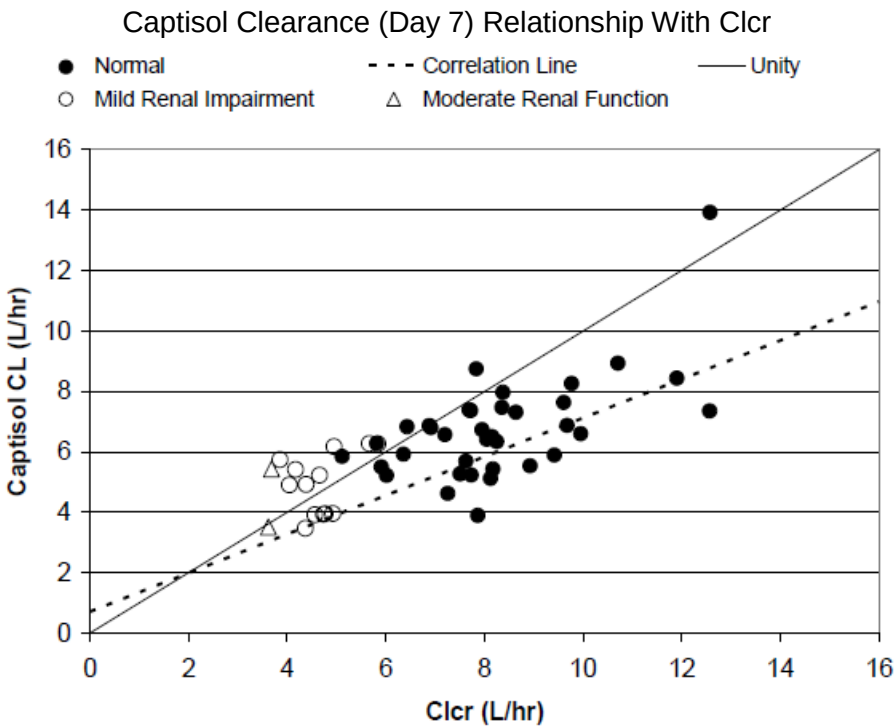
		Normal Renal Function				Mild Impairment				Moderate Impairment	
Infusion = 0.5 hr		Cohort = 2A				Cohort = 3A				Cohort = 4A	
		n	Mean	%CV	GeoMean	n	Mean	%CV	GeoMean	n	Mean
Dose	(mg)	16	5195	13.4	5151	9	3840	27.8	3705 b	1	2625
Dose	(mg/kg)	16	58.1	24.4	56.5	9	59.9	27.4	57.8	1	40.4
C _{max}	(ug/mL)	16	551	26.2	531	9	491	32.5	465	1	330
T _{max}	(hr)	16	0.474	7.9	0.472	9	0.496	21.6	0.487	1	0.483
C _{min}	(ug/mL)	16	23.5	54.9	19.6	9	31.0	44.5	27.8	1	38.9
C _{avg}	(ug/mL)	16	138	28.3	132	9	139	27.5	134	1	125
DFL		16	392	20.2	385	9	330	21.9	323	1	234
AUC _τ	(ug*hr/mL)	16	830	28.3	791	9	837	27.5	806	1	747
λ _z	(1/hr)	16	0.4594	17.3	0.4534	9	0.3949	20.2	0.3878	1	0.3424
t _{1/2}	(hr)	16	1.55	15.8	1.53	9	1.82	20.4	1.79	1	2.02
Cl	(L/hr)	16	6.73	31.7	6.51	9	4.67	19.3	4.60 b	1	3.51
CL/kg	(L/hr/kg)	16	0.0747	31.8	0.0714	9	0.0730	19.5	0.0717	1	0.0540
V _{ss}	(L)	16	11.5	20.5	11.2	9	10.2	13.3	10.1	1	9.65
V _{ss} /kg	(L/kg)	16	0.127	24.7	0.123	9	0.159	13.3	0.157 b	1	0.148
V _z	(L)	16	14.6	20.2	14.4	9	11.9	9.2	11.9 b	1	10.3
V _z /kg	(L/kg)	16	0.161	22.4	0.157	9	0.185	7.2	0.185 b	1	0.158
MRT	(hr)	16	1.77	22.2	1.73	9	2.25	22.9	2.20 b	1	2.75
Clcr	(L/hr)	16	8.39	19.6	8.25	9	4.66	11.4	4.63 b	1	3.62
Clcr/kg	(L/hr/kg)	16	0.0918	18.1	0.0904	9	0.0725	8.9	0.0722 b	1	0.0557
Infusion = 0.25 hr		Cohort = 2B				Cohort = 3B				Cohort = 4B	
		n	Mean	%CV	GeoMean	n	Mean	%CV	GeoMean	n	Mean
Dose	(mg)	19	5734	24.8	5570	7	4750	41.0	4339	1	4375
Dose	(mg/kg)	18	61.6	35.7	57.7	7	77.1	36.1	71.4	1	75.0
C _{max}	(ug/mL)	19	751	33.8	714 a	7	680	42.5	626	1	528
T _{max}	(hr)	19	0.228	10.9	0.226 a	7	0.233	0.0	0.233	1	0.233
C _{min}	(ug/mL)	19	31.0	61.3	25.9	6	34.3	64.1	30.0	1	28.1
C _{avg}	(ug/mL)	19	147	34.0	139	6	169	40.5	159	1	134
DFL		19	497	24.6	482 a	7	469	33.2	449 a	1	331
AUC _τ	(ug*hr/mL)	19	883	34.0	835	6	1015	40.5	957	1	804
λ _z	(1/hr)	19	0.4142	18.2	0.4076	6	0.4189	20.3	0.4122	1	0.4184
t _{1/2}	(hr)	19	1.73	19.0	1.70	6	1.71	18.3	1.68	1	1.66
Cl	(L/hr)	19	6.81	19.5	6.67	6	5.36	19.1	5.28 b	1	5.44
CL/kg	(L/hr/kg)	18	0.0708	24.6	0.0688	6	0.0897	28.5	0.0863	1	0.0932
V _{ss}	(L)	19	13.2	23.3	12.9 c	6	10.6	19.0	10.4 b	1	11.4
V _{ss} /kg	(L/kg)	18	0.138	19.2	0.136 c	6	0.175	25.2	0.171	1	0.196
V _z	(L)	19	16.7	22.0	16.4 a,c	6	12.9	15.5	12.8 b	1	13.0
V _z /kg	(L/kg)	18	0.174	18.4	0.171	6	0.213	21.8	0.209	1	0.223
MRT	(hr)	19	1.99	23.8	1.94 c	6	2.02	21.4	1.98	1	2.10
Clcr	(L/hr)	19	8.30	21.6	8.13	7	4.87	11.9	4.83 b	1	3.69
Clcr/kg	(L/hr/kg)	18	0.0855	12.9	0.0848	7	0.0803	14.4	0.0796	1	0.0632

(source: 15841a-report.pdf pg 21/42)

Captisol IV Cmax, AUC, Accumulation in Subjects with Normal Renal Function, or Mild Renal Impairment Receiving 15 or 30 Minute Infusion

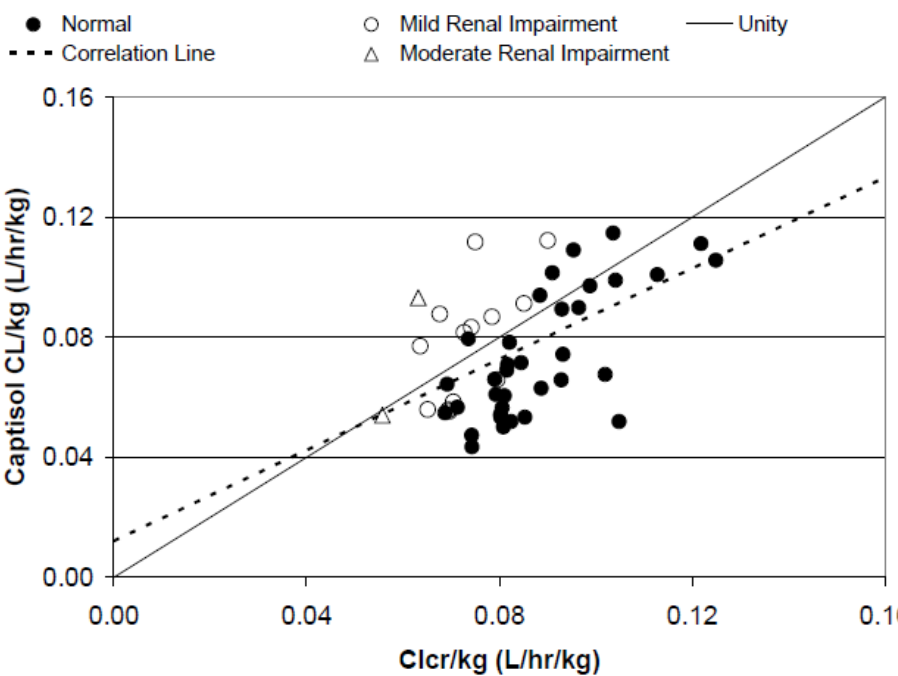
Infusion Rate = 0.5 hr					Infusion Rate = 0.25 hr				
Normal (2A) n=15					Normal (2B) n=19				
	Day1	Day 7	% Diff	Accum		Day1	Day 7	% Diff	Accum
Cmax	519 (23%)	551 (26%)	6.08%	1.061 (23%)		779 (31%)	751 (34%)	-1.83%	0.982 (22%)
AUC	723 (25%)	830 (28%)	13.3%	1.128 (14%)		832 (31%)	883 (34%)	6.57%	1.062 (15%)
Mild Impaired (3A) n=9					Mild Impaired (3B) n=7				
	Day1	Day 7	% Diff	Accum		Day1	Day 7	% Diff	Accum
Cmax	478 (30%)	491 (33%)	3.07%	1.031 (16%)		725 (49%)	680 (43%)	-3.84%	0.962 (12%)
AUC	741 (29%)	837 (27%)	14.1%	1.141 (11%)		833 (46%)	1015 (40%)	-4.53%	1.114 (11%)

(source: 15841a-report.pdf pg 22/42)



(source: 15841a-report.pdf pg 23/42)

Weight-Normalized Captisol Clearance (Day 7) Relationship With Weight-Normalized Clcr

	 (source: 15841a-report.pdf pg 24/42)
Conclusions	• Captisol t_{1/2} and CL on Day 7 were similar to Day 1 in subjects with normal or impaired renal function • Mild renal renal impairment displayed < 11% lower Captisol CL (L/hr/kg) compared to patients with normal renal function. This reduction in Captisol clearance is not considered clinically significant. • Accumulation ratios for AUC and C_{min} on Day 7 were low for both normal and renal impaired patients • Captisol CL was approximately linearly correlated with CRCL. Decreasing CRCL was associated with decreasing Captisol CL. • As the Captisol / CBZ ratio cannot be reduced, it is not feasible to reduce the Captisol dose without reducing the CBZ dose.
Comment	<i>Report 15841a contains all the analyses of report 15875a, but with additional conclusions. For this reason, the only report 15841a will be presented.</i> <i>As expected, the Captisol C_{max} is lower when infusing over a 30-minute duration compared to a 15-minute duration which is supportive of the 30-minute duration. Captisol clearance appears to decrease with decreasing creatinine clearance.</i> <i>Sponsor states that the 11% reduction in Captisol CL/kg in patients with mild RI compared to patients with normal renal function is not clinically significant. However, daily Captisol dose in Carbella (e.g. 28000 mg Captisol/day for a patient that was on 1600 mg oral CBZ / day) is substantially greater than other approved products (13440 mg Captisol/day for Vfend loading dose, 8960 mg Captisol for Vfend maintenance dose). In addition, there was a 53% increase in urinary N-acetyl-β-D-glucosaminidase (NAG) observed on Day 7 of Carbella therapy compared to baseline in all patients (indicative of damage to renal tubules). However, a Captisol dose-reduction in patients with impaired renal function may not be practical as it is apparently not feasible to reduce the Captisol/CBZ ratio, and thus reducing the Captisol dose would also reduce the CBZ dose (which may increase the risk of seizures).</i>

	<i>Please see the recommendations for section 8.6 of the Carbella label (Section “3. Labelling Recommendations” in this review) for details on monitoring for patients receiving Carbella. Use of Carbella in patients with moderate RI, severe RI, or ERSD is not recommended.</i>
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4.2.3 15926a: PK of Oral CBZ and IV CBZ formulation with Cavitron – NINDS Study

Study Report #	15926A
Title	Pharmacokinetic Evaluation of Intravenous Carbamazepine as a Parenteral Alternative for Replacement in Adult and Pediatric Subjects With Epilepsy for Whom Continuation of Oral Administration is Temporarily Not Feasible
Objectives	- Determine the bioavailability (F) of CBZ (CBZ) based on steady-state oral dosing and supplemental intravenous (IV) stable-labeled CBZ (SL-CBZ) formulated with 2-hydroxypropyl-β-cyclodextrin marketed under the name Cavitron. - Determine the pharmacokinetic (PK) parameters following single-dose IV administration of CBZ. - Predict steady-state IV concentrations of CBZ. - Determine optimal infusion duration to preserve CBZ concentrations within the therapeutic range and minimize adverse events.
Study Design	The Sponsor received CBZ PK data from The University of Minnesota that was obtained from a study conducted as part of The Epilepsy Program Project Grant (sponsored by NINDS). The NINDS study was an open-label single-dose PK study in patients that were already receiving oral CBZ therapy.
Dosing and Administration	Patients received a single infusion of 100 mg IV radio-labelled CBZ in the morning of the study visit. The patient then received a dose of oral CBZ that is 100 mg less than their standard oral CBZ dose in the morning (in order to ensure the total CBZ administration for the morning remains unchanged).
PK Assessment	PK samples were obtained at 0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, 72, and 96 hours after the end of the infusion.
Bioanalytical Methods	PK samples were analyzed using an LC-MS method. PK samples were run along with a 7-concentration standard curve (run in triplicate, range: 0.5–20 µg/ml for CBZ). Three quality control samples were each run in triplicate. Intra-assay variability was <5.0% for all standards, between-assay variation <5% for all standards except for the lowest standard (14.5%). Accuracy ranged from 83.7% to 102.6% for all standards. Quality-control samples were all within ≤10% with respect to variability
Population/ Demographics	N=76 epilepsy patients on oral CBZ therapy

Results

Table 4. Noncompartmental Analysis Pharmacokinetic Parameter Summary Statistics for Single-Dose Intravenous Administration of the Stable-Labeled Carbamazepine

Pharmacokinetic Parameter	N	Mean	SD	Min	Med	Max	%CV	Geometric Mean
$C_{\max, \text{sd}}$ (ug/mL)	76	2.03	0.723	0.690	1.86	4.14	35.5	1.91
$T_{\max, \text{sd}}$ (h)	76	0.621	0.656	0.0833	0.400	4.47	105.6	0.465
k_{el} (1/h)	76	0.0323	0.0148	0.0107	0.0281	0.0789	46.0	0.0294
$t_{1/2}$ (h)	76	25.8	11.2	8.79	24.6	64.6	43.3	23.6
$AUC_{0-\infty}$ (ug $\times$ h/mL)	76	38.2	15.3	14.9	36.5	94.5	40.1	35.7
CL (L/h)	76	3.15	1.17	1.16	2.88	7.27	37.0	2.96
Wt Norm. CL (L/h/kg)	76	0.0398	0.0153	0.0132	0.0360	0.0886	38.3	0.0371
V_z (L)	76	108	45.1	48.9	97.7	275	41.6	101
V_{ss} (L)	76	102	42.5	46.4	91.7	259	41.8	94.4
Wt Norm. V_{ss} (L/kg)	76	1.24	0.439	0.612	1.13	3.17	35.3	1.18

Abbreviations: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; CL, total plasma clearance; $C_{\max, \text{sd}}$, maximum plasma drug concentration after single dose; %CV, percent coefficient of variation; k_{el} , apparent first-order terminal elimination rate constant; Max, maximum; Med, median; Min, minimum; N, number of subjects; SD, standard deviation; $t_{1/2}$, terminal elimination phase half-life; $T_{\max, \text{sd}}$, time to reach maximum plasma drug concentration after single dose; V_{ss} , volume of distribution at steady state; V_z , volume of distribution based on the terminal phase; Wt Norm., weight normalized.

Table 5. Noncompartmental Analysis Pharmacokinetic Parameter Summary Statistics for Steady-State Oral Carbamazepine Administration

Variable	N	Mean	SD	Min	Med	Max	%CV	Geometric Mean
$C_{\max, \text{ss}}$ (ug/mL)	70 ^a	9.47	2.98	2.89	9.11	17.1	31.5	8.99
$T_{\max, \text{ss}}$ (h)	70	1.59	2.69	0.00	0.00	11.5	170	--
AUC_{τ} (ug $\times$ h/mL)	70	89.5	29.3	28.5	87.2	168	32.7	84.5
CL_{ss}/F (L/h)	70	3.56	1.88	0.687	3.70	10.3	52.9	3.06
Wt Norm. CL_{ss}/F (L/h/kg)	70	0.0448	0.0238	0.00869	0.0410	0.122	53.1	0.0384

Abbreviations: AUC_{τ} , area under the plasma concentration-time curve at steady state from time 0 to the end of the dosing interval; CL_{ss}/F , apparent total plasma clearance after extravascular administration; $C_{\max, \text{ss}}$, maximum plasma drug concentration at steady state; %CV, percent coefficient of variation; Max, maximum; Med, median; Min, minimum; N, number of subjects; SD, standard deviation; $T_{\max, \text{ss}}$, time to reach maximum plasma drug concentration at steady state; Wt Norm., weight normalized.

^a The oral dose was not administered to 6 subjects on the morning of the study.

Table 6. Summary Statistics for Carbamazepine Absolute Oral Bioavailability Calculation

Variable	N	Mean	SD	Min	Med	Max	%CV	Geometric Mean
Protocol dose (mg)	70 ^a	426	226	200	400	1200	53.0	376
Oral AUC_{τ} (ug $\times$ h/mL)	70	89.5	29.3	28.5	87.2	168	32.7	84.5
Intravenous dose (mg)	76	106	5.38	86.9	106	130	5.09	106
Intravenous $AUC_{0-\infty}$ (ug $\times$ h/mL)	76	38.2	15.3	14.9	36.5	94.5	40.1	35.7
Absolute bioavailability (all subjects)	70	0.742	0.287	0.348	0.670	1.65	38.7	0.693
Absolute bioavailability (twice daily subjects)	61	0.780	0.284	0.371	0.744	1.65	36.5	0.734

Abbreviations: AUC_{τ} , area under the plasma concentration-time curve at steady state from time 0 to the end of the dosing interval; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; %CV, percent coefficient of variation; Max, maximum; Med, median; Min, minimum; N, number of subjects; SD, standard deviation.

^a The oral dose was not administered to 6 subjects on the morning of the study.

	Predicted CBZ PK Profile After IV Infusion Over Various Infusion Durations Plasma Carbamazepine Conc. (mg/L) Time (hours) Duration (hrs) — 0.25 — 0.50 — 0.75 --- 1.00 2.00 - - - 3.00
Conclusions	- A 70% bioavailability is a reasonable value to use for an oral-to-IV conversion - Prolonging the infusion duration reduces C_{max} and may help mitigate the risk of adverse events
Comment	<i>The Sponsor conducted analyses of this data that was received from The University of Minnesota in order to determine the oral-to-IV conversion value for study OV-1015. The PK analyses are acceptable.</i> <i>Based on the results presented in this study, it was reasonable for the Sponsor to select the 70% oral-to-IV conversion when designing study OV-1015.</i>

4.2.4 OV-1015-MODSIM-V2 – Modeling and Simulation Report

Study Report #	OV-1015- MODSIM - V2 (April 2014)
Title	Additional exploratory analysis for pAUC resulting in changes in oral to IV conversion rate or IV dosing interval
Objectives	Conduct the following simulations (in response to a request from the Agency to utilize modelling and simulation in order to determine dosing schedule which may result in the maximum number of partial AUC and PK parameters contained within the 80% to 125% no-effect boundaries: 1. Increase the IV conversion factor from 70% to 75% of the total daily oral dose and keep the same dosing interval (ie, q6 hour) and infusion rate of 15 minutes or 30 minutes. 2. Increase the IV conversion factor from 70% to 80% of the total daily oral dose and keep the same dosing interval (ie, q6 hour) and infusion rate of 15 minutes or 30 minutes. 3. Investigate variable dosing interval (ie. from q6 hour to q4 hour) to see if derived partial AUC and PK parameters provide supporting evidence of enhanced bioequivalence than what is currently observed (70% every 6

	hour dosing interval) between the oral and IV formulations. • Increase the IV conversion factor from 70% to 75% of the total daily oral dose with the Q 4hr dosing interval and an infusion rate of 15 minutes or 30 minutes. • Increase the IV conversion factor from 70% to 80% of the total daily oral dose with the Q 4hr dosing interval and an infusion rate of 15 minutes or 30 minutes. 4. Evaluation of sample size effect utilizing a variety of methods including excluding subjects, modifying the profiles by resampling, and increasing the number of subjects by modeling/simulations 5. Search the literature for the comparison of fluctuations of CBZ exposures when switching among different oral formulations.
Statistical Analysis	Pharmacokinetic and statistical evaluations were performed with the software, Phoenix 64, WinNonLin version 6.3, Pharsight, Cary, NC. For constructing the partial AUCs for each time period for observed plasma concentrations, nominal times were used and estimates were based on applying a linear trapezoidal method. The following partial AUC values were estimated: AUC(0-2), AUC(2-4), AUC(4-6), AUC(0-6), AUC(6-8), AUC(8-10), AUC(10-12), AUC(12-14), AUC(14-16), AUC(16-18), AUC(18-20), AUC(20-22), and AUC(22-24). The partial AUCs were natural log transformed for comparison between oral and IV periods. Geometric least square means, the ratios of geometric means (IV versus oral), and the 90% confidence intervals (CIs) of these ratios were determined using a linear mixed-effect model with treatment (IV versus oral CBZ) as a fixed effect and subject as a random effect.
Population/ Demographics	Sponsor conducted PK simulations using PK parameter estimates derived from the PK data collected in study OV-1015 (see section 4.1.1).
PK Results	Figure 4.1.4.1: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 70% of the Daily Oral Dose Shaded bars indicate actual values obtained from CBZ plasma conc. vs. time data and non-shaded bars indicate values obtained by simulation. Red ovals show CI values outside the 80-120% range. (source: ov-1015-modsim-report-v2.pdf, pg 12/112) Figure 4.1.4.2: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ

pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 75% of the Daily Oral Dose

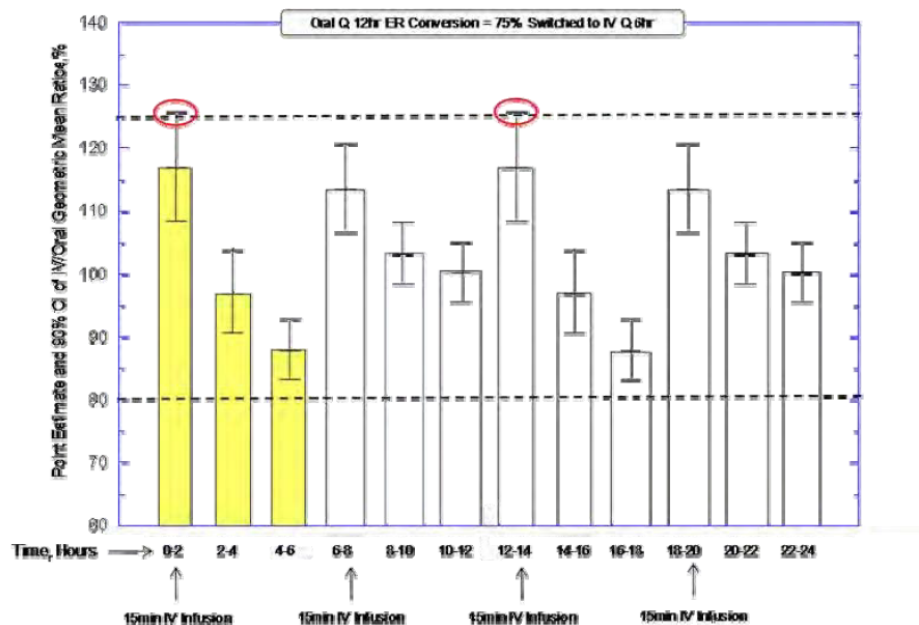


Figure 4.1.4.3: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 80% of the Daily Oral Dose

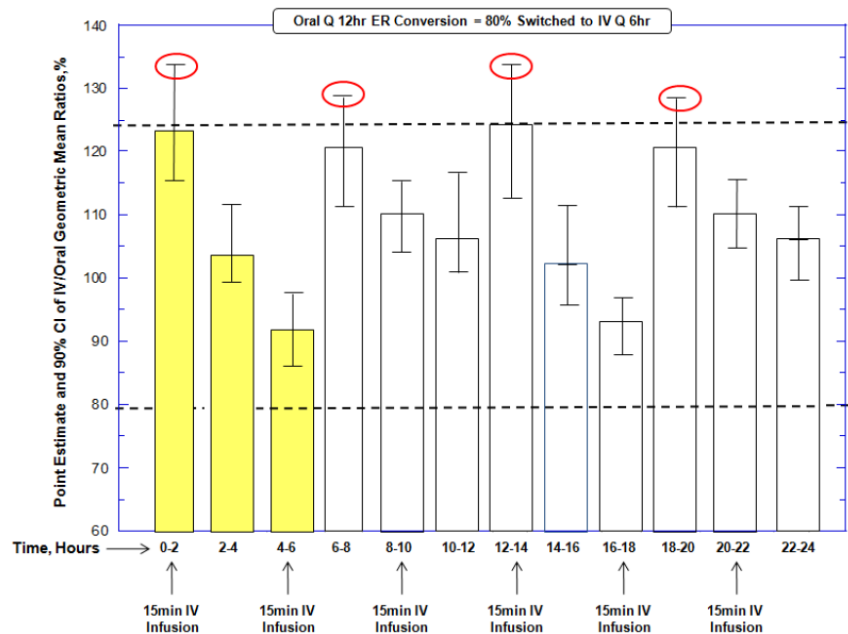


Figure 4.1.4.4: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 70% of the Daily Oral Dose

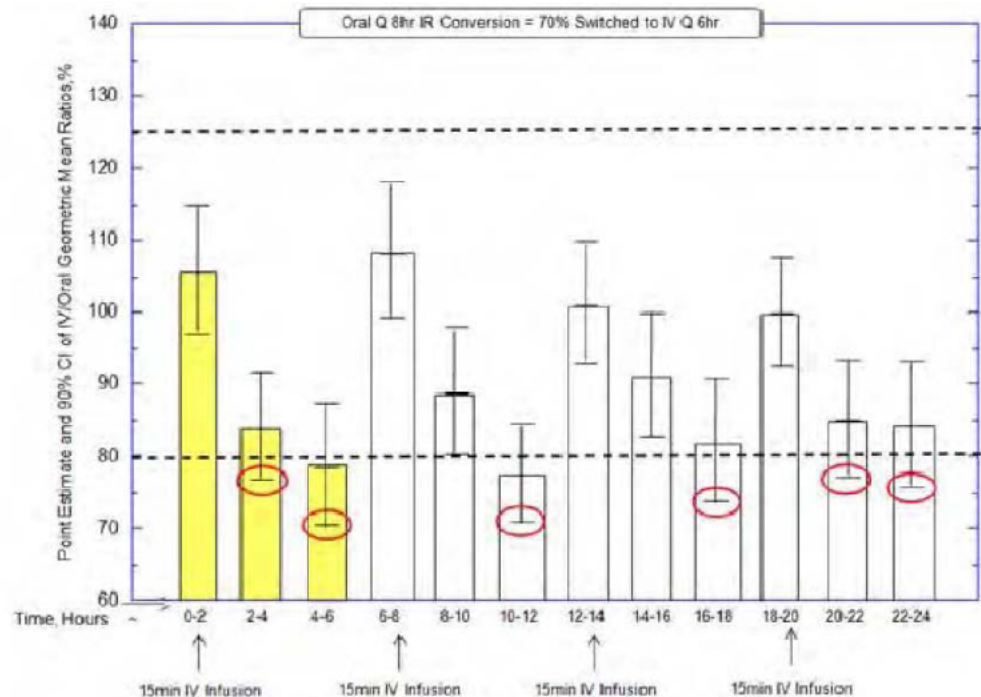


Figure 4.1.4.5: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 75% of the Daily Oral Dose

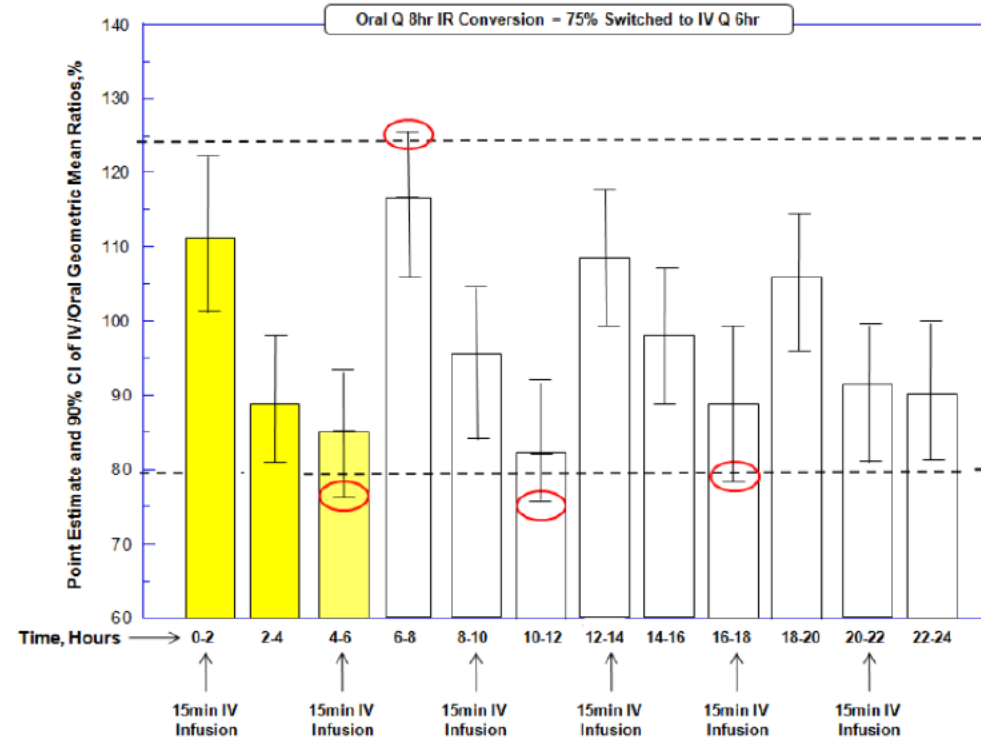


Figure 4.1.4.6: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q6h Over 15 minutes at the conversion rate of 80% of the Daily Oral Dose

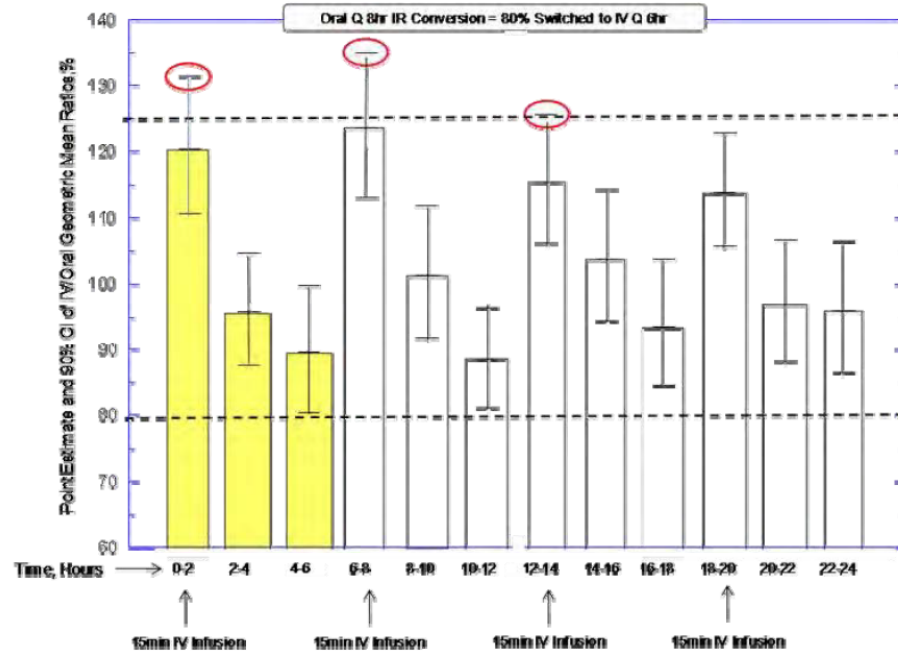


Table 4.1.4.1: Steady State Pharmacokinetic Parameters of CBZ Following Oral or Intravenous (IV) Administration of CBZ in Patients who were Previously Taking Immediate-Release (IR) (Q 8 hr) or Extended-Release (ER) (Q 12 hr) Oral Formulations of CBZ and then Switched to 15-Minutes (Upper Panel) or 30-Minutes (Lower Panel) IV Infusion of CBZ Given Q 6 hr at Oral to IV Dose Conversion Factors of 70%, 75% or 80%

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI L*	90%CI U*	PE	90%CI L	90%CI U	PE	90%CI L	90%CI U	PE	90%CI L	90%CI U
IR Q 8 hr (N = 12)	15 min Infusion Q 6 hr	70%	129.4	117.6	142.4	90.3	83.1	98.2	79.8	72.8	87.4	90.3	83.1	98.2
IR Q 8 hr (N = 12)	15 min Infusion Q 6 hr	75%	138.6	126.0	152.6	96.8	89.0	105.2	85.5	78.0	93.6	96.8	89.0	105.2
IR Q 8 hr (N = 12)	15 min Infusion Q 6 hr	80%	147.9	134.4	162.8	103.2	94.9	112.2	91.2	83.2	99.9	103.2	94.9	112.2
ER Q 12 hr (N = 28)	15 min Infusion Q 6 hr	70%	126.5	112.0	141.0	96.0	91.0	101.4	94.7	89.8	99.9	96.0	91.0	101.4
ER Q 12 hr (N = 28)	15 min Infusion Q 6 hr	75%	135.5	120.9	152.0	102.9	97.5	108.6	101.5	96.2	107.1	102.9	97.5	108.6
ER Q 12 hr (N = 28)	15 min Infusion Q 6 hr	80%	144.6	128.9	162.1	109.8	104	115.8	108.2	102.6	114.2	109.8	104	115.8

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug*hr/mL		
			PE*	90%CI L*	90%CI U*	PE	90%CI L	90%CI U	PE	90%CI L	90%CI U	PE	90%CI L	90%CI U
IR Q 8 hr (N = 6)	30 min Infusion Q 6 hr	70%	99.0	87.7	111.8	87.5	79.6	96.3	83.0	72.0	94.7	87.5	79.6	96.3
IR Q 8 hr (N = 6)	30 min Infusion Q 6 hr	75%	106.0	93.9	119.7	93.8	85.2	103.2	88.9	78.0	101.5	93.8	85.2	103.2
IR Q 8 hr (N = 6)	30 min Infusion Q 6 hr	80%	113.1	100.2	127.7	100.1	90.9	110.1	94.9	83.2	108.2	100.1	90.9	110.1
ER Q 12 hr (N = 17)	30 min Infusion Q 6 hr	70%	113.0	101.4	126.1	94.8	86.3	104.2	91.5	83.3	100.5	94.8	86.3	104.2
ER Q 12 hr (N = 17)	30 min Infusion Q 6 hr	75%	121.1	108.6	135.1	101.6	92.5	111.6	98.0	89.3	107.6	101.6	92.5	111.6
ER Q 12 hr (N = 17)	30 min Infusion Q 6 hr	80%	129.2	115.8	144.1	108.4	98.6	119.1	104.6	95.2	114.8	108.4	98.6	119.1

(source: ov-1015-modsim-report-v2.pdf, pg 19/112)

Figure 4.1.4.7: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q4h Over 15 minutes at the conversion rate of 70% of the Daily Oral Dose

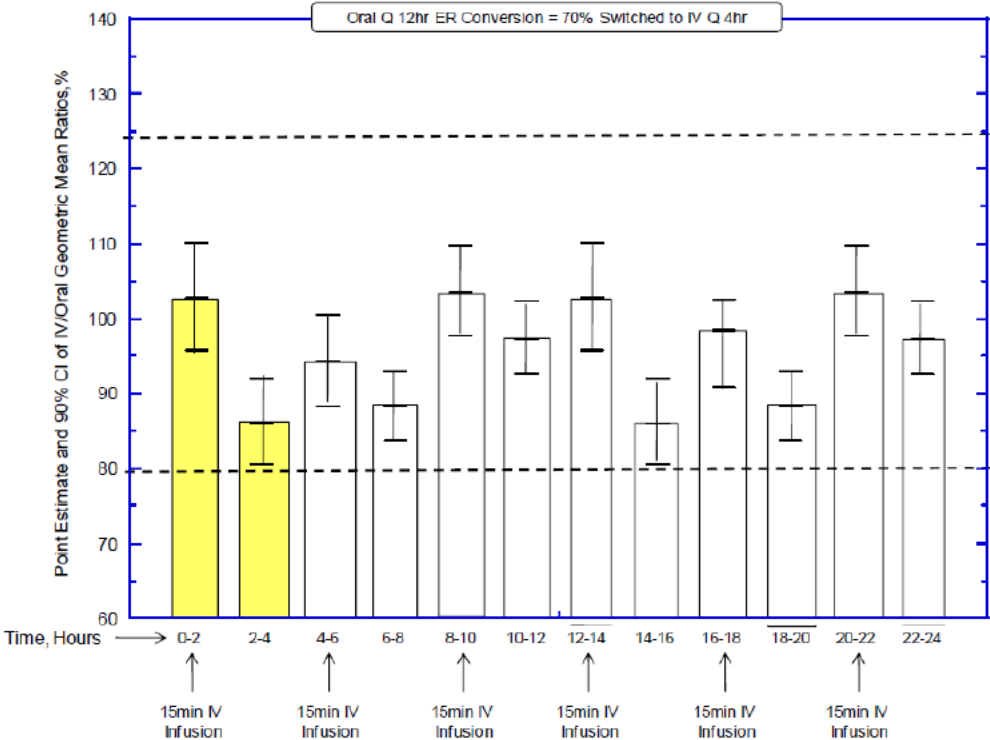


Figure 4.1.4.8: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q4h Over 15 minutes at the conversion rate of 75% of the Daily Oral Dose

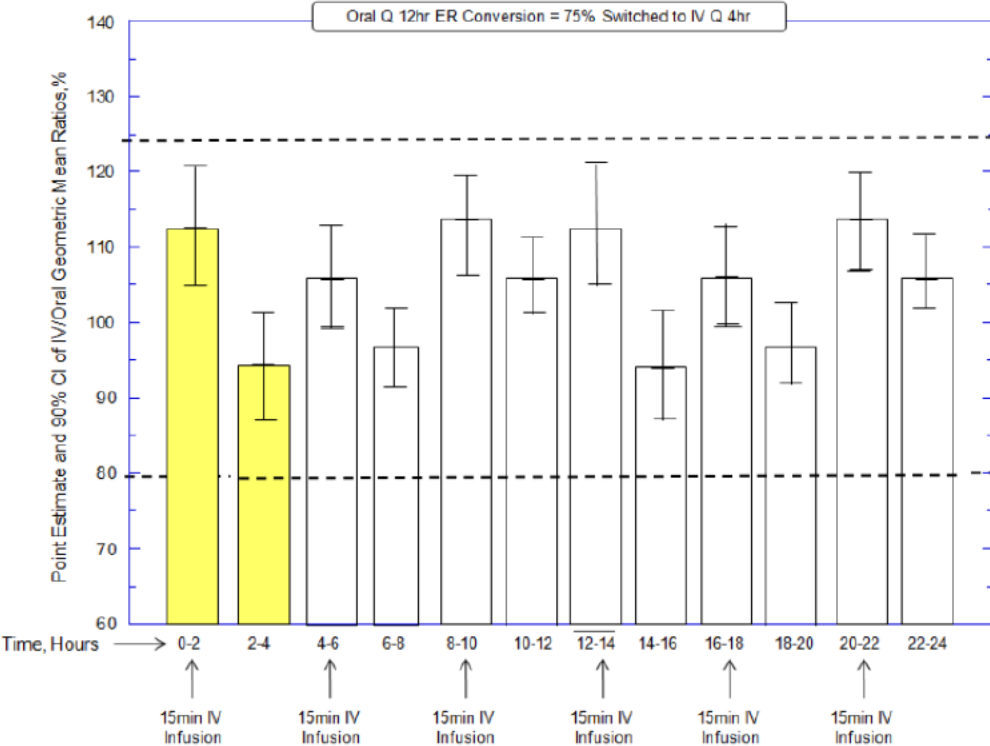


Figure 4.1.4.9: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q12h oral CBZ (XR) to IV CBZ infusion Q4h

Over 15 minutes at the conversion rate of 80% of the Daily Oral Dose

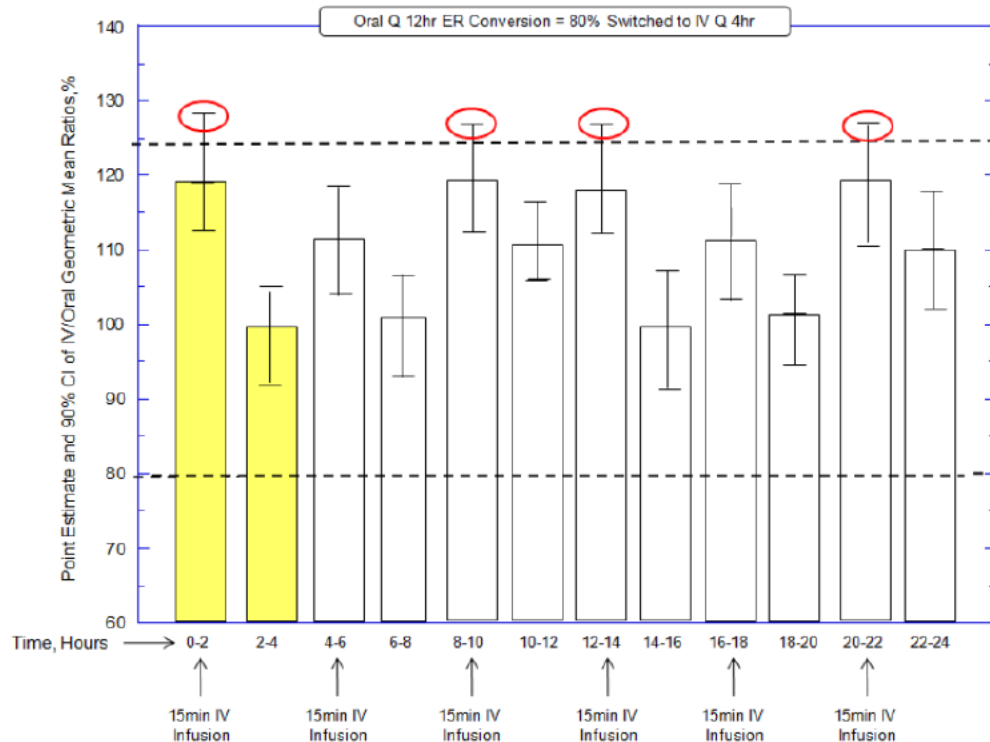


Figure 4.1.4.10: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q4h Over 15 minutes at the conversion rate of 70% of the Daily Oral Dose

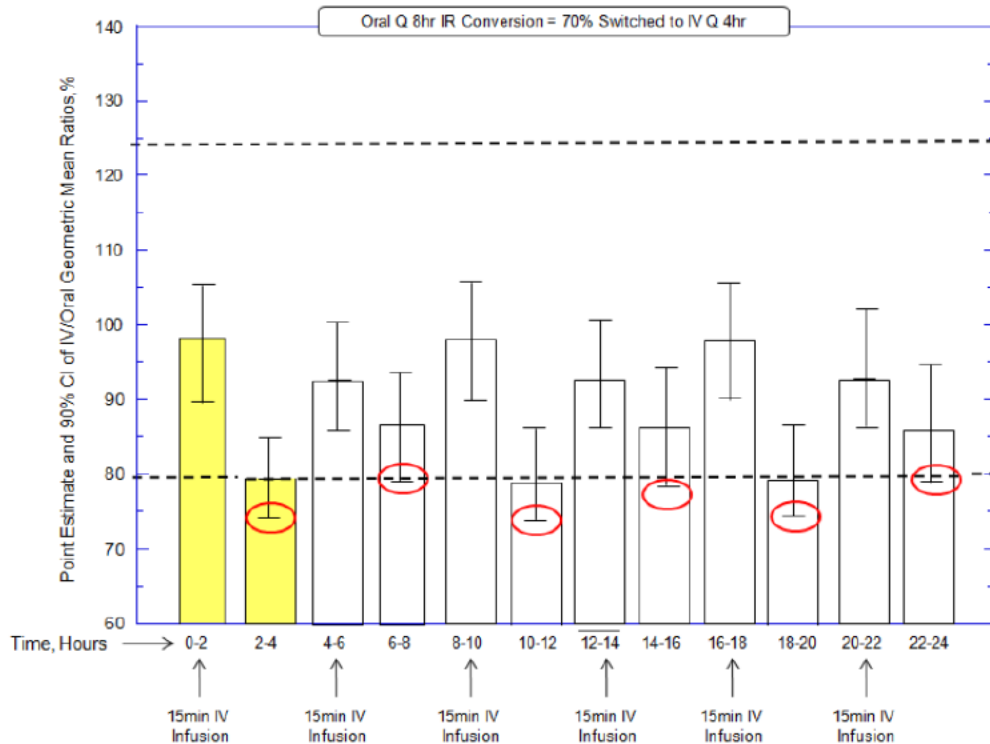


Figure 4.1.4.11: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q4h Over 15 minutes at the conversion rate of 80% of the Daily Oral Dose

15 minutes at the conversion rate of 75% of the Daily Oral Dose

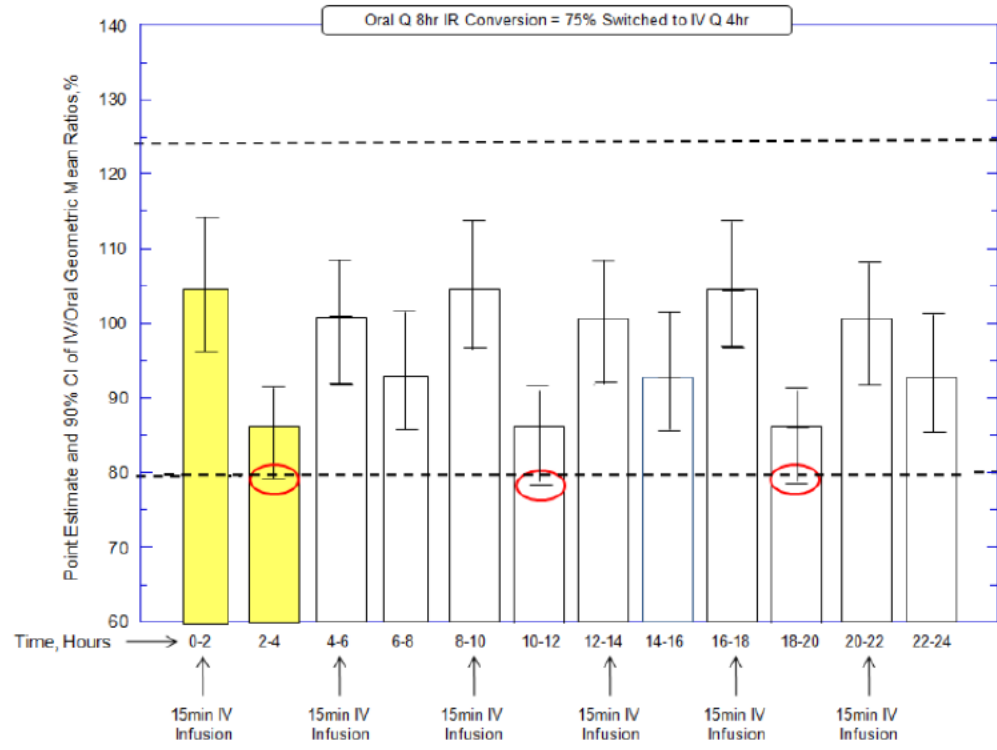


Figure 4.1.4.12: Point Estimate and 90% CI of IV/Oral GM Ratios (n=28) for CBZ pAUC in patients switching from Q8h oral CBZ (IR) to IV CBZ infusion Q4h Over 15 minutes at the conversion rate of 80% of the Daily Oral Dose

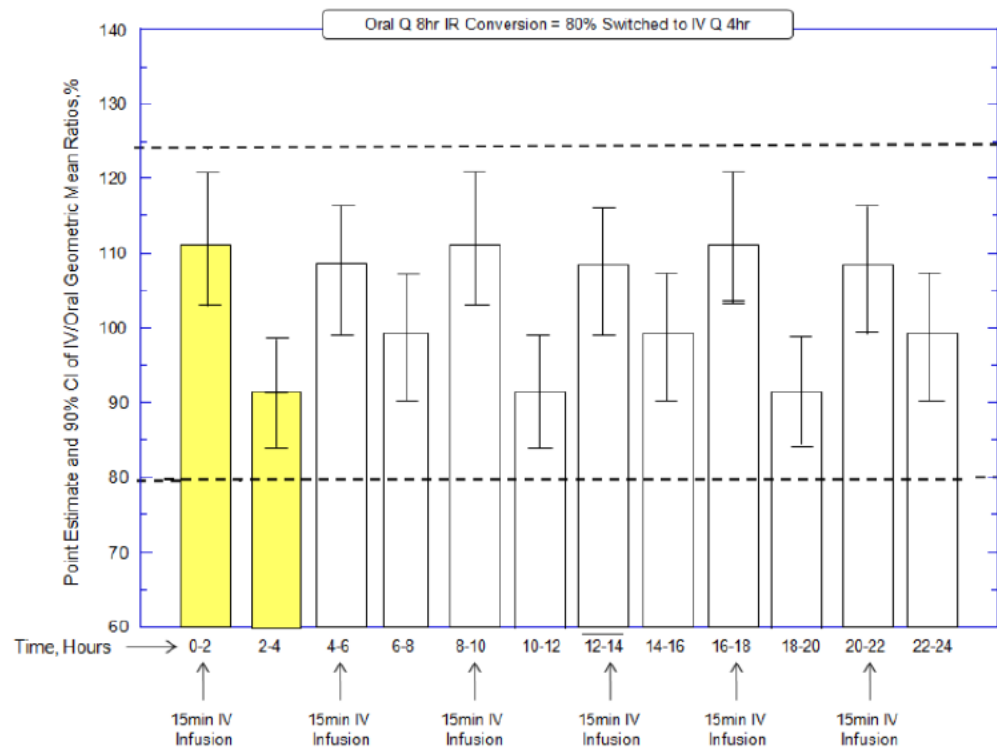


Table 4.1.4.2: Model Derived Steady State Pharmacokinetic Parameters of CBZ Following Oral or Intravenous (IV) Administration of CBZ in Patients who were

Previously Taking Immediate-Release (IR) (Q 8 hr) or Extended-Release (ER) (Q 12 hr) Oral Formulations of CBZ and then Switched to 15-Minutes (Upper Panel) or 30-Minutes (Lower Panel) IV Infusion of CBZ Given Q 4 hr at Oral to IV Dose Conversion Factors of 70%, 75% or 80%

Oral Dosage Form	IV Infusion	Oral to IV Conversion Factor	Steady State Pharmacokinetic Parameters											
			C _{max} , ug/mL			C _{avg} , ug/mL			C _{min} , ug/mL			AUC (0-24), ug/hr/mL		
			PE*	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U
IR Q 8 hr (N = 6)	30 min Infusion Q 4 hr	70%	89.6	81.5	98.4	87.0	79.3	95.5	91.1	82.6	100.6	87.0	79.3	95.5
IR Q 8 hr (N = 6)	30 min Infusion Q 4 hr	75%	95.7	87.4	105.4	93.2	84.9	102.3	97.7	88.5	107.8	93.2	84.9	102.3
IR Q 8 hr (N = 6)	30 min Infusion Q 4 hr	80%	102.3	93.2	112.4	99.5	90.6	109.2	104.2	94.4	115.0	99.5	90.6	109.2
ER Q 12 hr (N = 17)	30 min Infusion Q 4 hr	70%	90.5	89.9	100.0	94.7	86.6	103.7	99.9	91.5	109.2	94.7	86.6	103.7
ER Q 12 hr (N = 17)	30 min Infusion Q 4 hr	75%	105.6	96.3	115.7	101.5	92.7	111.1	107.1	98.0	117	101.5	92.7	111.1
ER Q 12 hr (N = 17)	30 min Infusion Q 4 hr	80%	112.6	102.8	123.4	108.3	98.9	118.5	114.2	104.5	124.8	108.3	98.9	118.5

(source: ov-1015-modsim-report-v2.pdf, pg 30/112)

Figure 4.1.4.3: Pharmacokinetic Model Derived Partial AUC Values of CBZ Following Oral or Intravenous (IV) Administration of CBZ in Patients who were Previously Taking Immediate-Release (IR) (Q 8 hr) or Extended-Release (ER) (Q 12 hr) Oral Formulations of CBZ and then Switched to 15-Minutes (Upper Panel) or 30-Minutes (Lower Panel) IV Infusions of CBZ Given Q 4 hr at Oral to IV Dose Conversion Factors of 70%, 75% or 80%

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR, 15-Minute IV Infusion Q 4 hr (N = 12)									Oral Dose = Q 12 hr ER, 15-Minute IV Infusion Q 4 hr (N = 28)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U
0 - 2 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	104.5	97.4	112.1	112.0	104.4	120.2	119.5	111.3	128.2
2 - 4 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	87.1	81.2	93.5	93.4	86.9	100.2	99.6	92.7	106.9
4 - 6 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	98.2	92.3	104.5	105.2	98.9	112.0	112.3	105.5	119.5
6 - 8 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	89.3	84.6	94.2	95.6	90.6	101.0	102.0	96.6	107.7
8 - 10 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	105.3	99.5	111.6	112.9	106.6	119.5	120.4	113.7	127.5
10 - 12 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	98.5	93.8	103.4	105.5	100.5	110.8	112.5	107.2	118.2
12 - 14 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	104.5	97.4	112.1	112.0	104.4	120.2	119.5	111.3	128.2
14 - 16 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	87.1	81.2	93.5	93.4	86.9	100.2	99.6	92.7	106.9
16 - 18 hr	97.8	90.0	106.3	104.8	96.5	113.9	111.8	102.9	121.5	98.2	92.3	104.5	105.2	98.9	112.0	112.3	105.5	119.5
18 - 20 hr	79.9	74.0	86.3	85.6	79.3	92.5	91.3	84.6	98.6	89.3	84.6	94.2	95.6	90.6	101.0	102.0	96.6	107.7
20 - 22 hr	93.7	86.5	101.5	100.4	92.6	108.8	107.1	98.8	116.1	105.3	99.5	111.6	112.9	106.6	119.5	120.4	113.7	127.5
22 - 24 hr	86.7	79.3	94.7	92.9	85.0	101.5	99.1	90.7	108.3	98.5	93.8	103.2	105.5	100.5	110.8	112.5	107.2	118.2

Partial AUC (ug*hr/mL)	Oral Dose = Q 8 hr IR, 30-Minute IV Infusion Q 4 hr (N = 6)									Oral Dose = Q 12 hr ER, 30-Minute IV Infusion Q 4 hr (N = 17)								
	Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%			Oral to IV Conversion = 70%			Oral to IV Conversion = 75%			Oral to IV Conversion = 80%		
	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U	PE	90%CI _L	90%CI _U
0 - 2 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	102.7	94.5	111.7	110.1	101.2	119.7	117.4	108.0	127.7
2 - 4 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	86.5	78.3	95.5	92.6	83.9	102.3	98.8	89.5	109.1
4 - 6 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	96.8	87.7	106.8	103.7	93.9	114.4	110.6	100.2	122.1
6 - 8 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	88.0	79.9	97.1	94.3	85.6	104.0	100.6	91.3	110.9
8 - 10 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	101.8	93.3	111.1	109.1	100.0	119.1	116.4	106.4	127.0
10 - 12 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	93.9	85.4	103.2	100.6	91.5	110.6	107.3	97.6	118.0
12 - 14 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	102.7	94.5	111.7	110.1	101.2	119.7	117.4	108.0	127.7
14 - 16 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	86.5	78.3	95.5	92.6	83.9	102.3	98.8	89.5	109.1
16 - 18 hr	97.0	87.4	107.5	103.9	93.7	115.2	110.8	99.9	122.9	96.8	87.7	106.8	103.7	93.9	114.4	110.6	100.2	122.1
18 - 20 hr	75.9	66.8	86.3	81.3	71.6	92.4	86.8	76.4	98.6	88.0	79.9	97.1	94.3	85.6	104.0	100.6	91.3	110.9
20 - 22 hr	90.7	82.8	99.4	97.2	88.7	106.5	103.7	94.6	113.6	101.8	93.3	111.1	109.1	100.0	119.1	116.4	106.7	127.0
22 - 24 hr	86.1	76.1	97.4	92.3	81.6	104.3	98.4	87.0	111.3	93.9	85.4	103.2	100.6	91.5	110.6	107.3	97.6	118.0

(source: ov-1015-modsim-report-v2.pdf, pg 32/112)

Conclusions

- Based upon both partial AUC and PK parameters, only one of the IV infusion regimens was bioequivalent to the oral dose regimens based upon the 90% CI falling within 80-125% boundaries (Q 4hr IV interval, 75% conversion factor for oral ER infused over 30 minutes).
- Three of the Q 4hr IV dosing intervals (75% conversion factor for both oral IR and ER infused over 15 minutes, or 75% conversion factor for oral ER infused over 30 minutes)

	• one of the Q6 hr IV dosing intervals (75% conversion factor for oral ER infused over 15 min) provided acceptable (pAUC in combination with C_{max}, C_{min} and C_{avg}) alternative infusion regimens. • The 15 minute infusion rate along with the 75% conversion factor provided more partial AUC values within the 80-125% CI than the 30 minute infusion.
Comment	<i>PK simulations administering Carbella q4h instead of q6h demonstrated that the C_{max} can be lowered but the IV C_{min} value is less affected. However, due to concerns regarding hospital logistics, the q6h interval is the recommended interval (see section 4.1.2 for details).</i> (b) (4) <i>due to CMC concerns, the 70% oral-to-IV conversion is the recommended conversion value (see section 4.1.2 for details). The 30-minute infusion duration is the recommended infusion duration (see section 4.1.2 for details).</i>

4.3 NONMEM Code for Sponsor's Final Population PK Model

\$SUBROUTINES ADVAN3 TRANS4

\$PK

CL=THETA(1)*EXP(ETA(1))

V1=THETA(2)*EXP(ETA(2))

Q=THETA(3)

V2=THETA(4)*EXP(ETA(3))

K=CL/V1

K12=Q/V1

K21=Q/V2

S1=V1

\$THETA (0.1,5,200) (1,20,100) (1,200,900) (10,200,2000)

\$OMEGA 0.25

\$OMEGA BLOCK (2) 0.25 0.10 0.25

\$ERROR

IPRED=F

W=F

IRES=DV-IPRED

IWRES=IRES/W

Y=IPRED+W*EPS(1)

\$SIGMA .5

\$EST MAXEVAL=5000 METHOD=CONDITIONAL INTERACTION PRINT=5 NOABORT

\$COV PRINT=E

This model was built using OV-1015 PK data.

4.4 OCP Filing Memo

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
NDA Number	206,030 (0000)	Brand Name	Carbella
OCP Division (I, II, III)	DCP-I	Generic Name	Carbamazepine
Medical Division	DNP	Drug Class	Dibenzazepine anticonvulsant
OCP Reviewer	Michael Bewernitz, Ph.D.	Indication(s)	An anti-epileptic drug indicated as replacement therapy in adults (18 years and older) when oral carbamazepine administration is temporarily not feasible
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Injectable solution for infusion
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.		
Pharmacometrics Team Leader	Kevin Krudys, Ph.D.		
Date of Submission	12/23/2013	Route of Administration	IV Infusion
Estimated Due Date of OCP Review	08/18/2014	Sponsor	Lundbeck, LLC.
Division Due Date	08/25/2014	Priority Classification	S
PDUFA Due Date	10/23/2014		

Clin. Pharm. and Biopharm. Information

This NDA application for Carbella (carbamazepine [CBZ] 10 mg/mL solution for injection) was submitted under section 505(b)(2) of the FDCA. The proposed indication is “replacement therapy in adult epilepsy patients when oral CBZ administration is temporarily not feasible”. Carbella injection was granted Orphan Drug Designation (# 08-2655) on June 27th, 2013. Carbella is intended to be commercialized as an IV infusion with a proposed dose of 70% of the oral dose. CBZ was originally approved in 1968 (as Tegretol tablets).

Sponsor has submitted 2 clinical studies, published literature, and previous findings of safety and efficacy to support bioequivalence with the reference listed drugs Tegretol® IR (200 mg tablet, NDA 16608) and Tegretol® XR (400 mg tablet, NDA 20234).

Phase 3 Studies

OV-1015 (PK Comparison and Safety Study, n=98): An open-label study to compare the steady-state PK of IV CBZ (70% of total oral daily dose, as 4 divided doses administered q6h) infused over various durations with oral CBZ PK in adult epilepsy patients over a 7-day duration. PK in a patient subset with mild or moderate renal impairment was also assessed.

13181A (Safety Study, n=105): An open-label study to assess safety and tolerability of IV CBZ (70% of total oral daily dose, as 4 divided doses q6h) infused over a 30 minute duration.

Reports of PK Analyses

15926A (PK of CBZ from a previous study): Report of analyses assessing oral CBZ bioavailability, prediction of steady-state CBZ concentrations after multiple IV infusions, and assessing the effect of infusion duration on CBZ concentrations using CBZ PK data acquired from a previous study (NINDS-01).

15875a (PK of captisol in OV-1015): Report of results from assessments of the effect of renal impairment on captisol PK using data acquired in study OV-1015.

15841a (PK of captisol in OV-1015): A supplemental report of the effect of renal impairment on captisol PK using data acquired in study OV-1015 including results from subgroup analyses stratified by infusion duration.

OV-1015-pAUC (pAUC BE of CBZ): Report of results from bioequivalence assessments of partial AUC using CBZ PK data acquired from study OV-1015.

OV-1015-MODSIM (pAUC BE of simulated CBZ): Report of results from bioequivalence assessments of partial AUC using simulated CBZ PK data.

OV-1015-suppha (effect of infusion duration on PK): Report of analyses assessing the effect of infusion duration on concentrations of CBZ, CBZ-epoxide (active metabolite), and total CBZ (CBZ+CBZ-epoxide).

Please refer to Appendices 1 and 2 for information on other studies included in this submission.

<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Annotated and clean versions of the label are included.
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				
single dose:	-			
multiple dose:	-			
Patients-				
single dose:	-			
multiple dose:	X	1		Study OV-1015 compared the steady-state PK of IV CBZ to oral CBZ as well as safety and tolerability in patients with epilepsy.
Dose proportionality -				
fasting / non-fasting single dose:	-			

fasting / non-fasting multiple dose:	-			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:				
gender:	-			
pediatrics:	-			
geriatrics:	-			
Renal impairment:	-			
Hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -	-			
solution as reference:	-			
alternate formulation as reference:	-			
Bioequivalence studies -	-			
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			

Food-drug interaction studies:				
Dissolution:	-			
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			Orphan drug designation for intravascular carbamazepine was granted on June 27th, 2013. As such, this drug is currently excused from PREA requirements.
Literature References	-			
Total Number of Studies		7		- 1 PK (Phase-3) - 6 PK analysis reports (15926a, 15875a, 15841a, OV-1015-pAUC, OV-1015-MODSIM, OV-1015-SuppBA)
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments sent to firm?	-			
QBR questions (key issues to be considered)	1. Have the analytical methods been sufficiently validated? 2. Is the IV CBZ bioequivalent to oral CBZ? 3. Are the proposed dosing regimens acceptable? 4. Are the label statements acceptable?			
Other comments or information not included above	---			

Primary reviewer Signature and Date	Michael Bewernitz
Secondary reviewer Signature and Date	Angela Yuxin Men

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Sponsor has provided results of bioequivalence assessment between the IV CBZ solution, IR CBZ, and ER CBZ.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	The Agency agreed to a 505(b)(2) submission pathway.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Define files are were not provided for the following datasets: cbz-auc-70-75-80.xls, cbzindparadose.xls, cbzpartial-aucs4.xls, cbzsimconq4.xls. An IR was sent to request define files for these studies.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product	X			

	(i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan status was granted.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___Yes___

A DSI inspection will be requested for the clinical and bioanalytical portions of study OV-1015.

[Reviewer comment: After additional internal discussions, it was determined that an inspection was not required for study OV-1015 as it was not a true bioequivalence study (due to the fact that two different formulations were being compared).]

The following comments were conveyed to the Sponsor in the 74-day letter:

1. Definition Files: Please provide a definition file for each of the following files:

- *cbz-auc-70-75-80.xls*
- *cbzindparadose.xls*
- *cbzpartial-aucs4.xls*
- *cbzsimconcq4.xls*

*In each definition file, please include variable descriptions and, where applicable, units of measurement. In addition, please clarify the location of the simulated data representing the 75% and 80% oral dose conversion within the *cbz-auc-70-75-80.xls* file (only simulated data representing the 70% oral dose conversion data could be found). If the simulated data representing the 75% or 80% oral dose conversion were not included in the NDA submission, please submit them. Also, file *cbzsimconcq4.xls* appears to contain simulated concentrations for a single q4h IV infusion. Please re-submit *cbzsimconcq4.xls* with simulated concentrations for the full week of treatment (Day 1 to Day 7) for each subject using the corresponding q4h IV infusion regimen.*

*In addition, please include any relevant PK simulation parameters in the *adpc.xpt* dataset for study ov-1015-pauc (e.g., oral-to-IV dose conversion value, IV infusion interval [e.g., q4hr, q6hr], etc.) and resubmit this dataset.*

2. Project Files: Please submit Pharsight Phoenix project files (e.g., *.phxproj), input datasets, output datasets (e.g., individual simulated PK values) and any other files that are relevant to the IV infusion simulations. Also, please provide any scripts, spreadsheets, or other files relevant to the computation of any AUC values (for example, the partial AUC values) derived from the aforementioned simulated IV PK data.

3. New Simulations: The PK simulation results shown in Figure 6 on page 13 in the OV-1015-MODSIM report demonstrate that the partial AUC 90% CI is expected to fall outside of the 80-125% range at various time points when switching to IV from oral IR q8hr carbamazepine. We recommend you conduct PK simulations to explore the feasibility of utilizing different dosing regimens and/or infusion parameters with a goal of producing an IV infusion concentration profile that meeting bioequivalence based on partial AUC after oral IR q8h carbamazepine and oral ER q12h carbamazepine. We also recommend assessing the bioequivalence of C_{max} and C_{min} for this alternative IV infusion regimen in comparison with oral IR q8h carbamazepine as well as oral ER q12h carbamazepine.

It is possible the simulated PK data for the alternate IV infusion regimen may not achieve bioequivalence at every time point for the aforementioned exposure metrics for oral IR q8h and/or oral ER q12h carbamazepine. If so, and if you do not expect the alternate IV infusion regimen to result in a clinically significant worsening of efficacy or safety, please provide your justification.

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

/s/

MICHAEL A BEWERNITZ
10/16/2014

VENKATESH A BHATTARAM
10/16/2014

YUXIN MEN
10/16/2014

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	206,030 (0000)	Brand Name	Carbella
OCP Division (I, II, III)	DCP-I	Generic Name	Carbamazepine
Medical Division	DNP	Drug Class	Dibenzazepine anticonvulsant
OCP Reviewer	Michael Bewernitz, Ph.D.	Indication(s)	An anti-epileptic drug indicated as replacement therapy in adults (18 years and older) when oral carbamazepine administration is temporarily not feasible
OCP Team Leader	Angela Yuxin Men, M.D., Ph.D.	Dosage Form	Injectable solution for infusion
Pharmacometrics Reviewer	Atul Bhattaram, Ph.D.		
Pharmacometrics Team Leader	Kevin Krudys, Ph.D.		
Date of Submission	12/23/2013	Route of Administration	IV Infusion
Estimated Due Date of OCP Review	08/18/2014	Sponsor	Lundbeck, LLC.
Division Due Date	08/25/2014	Priority Classification	S
PDUFA Due Date	10/23/2014		

Clin. Pharm. and Biopharm. Information

This NDA application for Carbella (carbamazepine [CBZ] 10 mg/mL solution for injection) was submitted under section 505(b)(2) of the FFDCA. The proposed indication is “replacement therapy in adult epilepsy patients when oral CBZ administration is temporarily not feasible”. Carbella injection was granted Orphan Drug Designation (# 08-2655) on June 27th, 2013. Carbella is intended to be commercialized as an IV infusion with a proposed dose of 70% of the oral dose. CBZ was originally approved in 1968 (as Tegretol tablets).

Sponsor has submitted 2 clinical studies, published literature, and previous findings of safety and efficacy to support bioequivalence with the reference listed drugs Tegretol® IR (200 mg tablet, NDA 16608) and Tegretol® XR (400 mg tablet, NDA 20234).

Phase 3 Studies

OV-1015 (PK Comparison and Safety Study, n=98): An open-label study to compare the steady-state PK of IV CBZ (70% of total oral daily dose, as 4 divided doses administered q6h) infused over various durations with oral CBZ PK in adult epilepsy patients over a 7-day duration. PK in a patient subset with mild or moderate renal impairment was also assessed.

13181A (Safety Study, n=105): An open-label study to assess safety and tolerability of IV CBZ (70% of total oral daily dose, as 4 divided doses q6h) infused over a 30 minute duration.

Reports of PK Analyses

15926A (PK of CBZ from a previous study): Report of analyses assessing oral CBZ bioavailability, prediction of steady-state CBZ concentrations after multiple IV infusions, and assessing the effect of infusion duration on CBZ concentrations using CBZ PK data acquired from a previous study (NINDS-01).

15875a (PK of captisol in OV-1015): Report of results from assessments of the effect of renal impairment on captisol PK using data acquired in study OV-1015.

15841a (PK of captisol in OV-1015): A supplemental report of the effect of renal impairment on captisol PK using data acquired in study OV-1015 including results from subgroup analyses stratified by infusion duration.

OV-1015-pAUC (pAUC BE of CBZ): Report of results from bioequivalence assessments of partial AUC using CBZ PK data acquired from study OV-1015.

OV-1015-MODSIM (pAUC BE of simulated CBZ): Report of results from bioequivalence assessments of partial AUC using simulated CBZ PK data.

OV-1015-suppb (effect of infusion duration on PK): Report of analyses assessing the effect of infusion duration on concentrations of CBZ, CBZ-epoxide (active metabolite), and total CBZ (CBZ+CBZ-epoxide).

Please refer to Appendices 1 and 2 for information on other studies included in this submission.

<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Annotated and clean versions of the label are included.
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				
single dose:	-			
multiple dose:	-			
Patients-				
single dose:	-			
multiple dose:	X	1		Study OV-1015 compared the steady-state PK of IV CBZ to oral CBZ as well as safety and tolerability in patients with epilepsy.
Dose proportionality -				
fasting / non-fasting single dose:	-			
fasting / non-fasting multiple dose:	-			
Drug-drug interaction studies -				

In-vivo effects on primary drug:	-			
In-vitro:	-			
Subpopulation studies -				
ethnicity:				
gender:	-			
pediatrics:	-			
geriatrics:	-			
Renal impairment:	-			
Hepatic impairment:	-			
PD:				
Phase 2:	-			
Phase 3:	-			
PK/PD:				
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
Population Analyses -				
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics				
Absolute bioavailability:	-			
Relative bioavailability -	-			
solution as reference:	-			
alternate formulation as reference:	-			
Bioequivalence studies -	-			
traditional design; single / multi dose:	-			
replicate design; single / multi dose:	-			
Food-drug interaction studies:				
Dissolution:	-			
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			

III. Other CPB Studies							
Genotype/phenotype studies:	-						
Chronopharmacokinetics	-						
Pediatric development plan	-			Orphan drug designation for intravascular carbamazepine was granted on June 27th, 2013. As such, this drug is currently excused from PREA requirements.			
Literature References	-						
Total Number of Studies		7		- 1 PK (Phase-3) - 6 PK analysis reports (15926a, 15875a, 15841a, OV-1015-pAUC, OV-1015-MODSIM, OV-1015-SuppBA)			
Filability and QBR comments							
	"X" if yes	Comments					
Application filable?	X						
Comments sent to firm?	-						
QBR questions (key issues to be considered)	1. Have the analytical methods been sufficiently validated? 2. Is the IV CBZ bioequivalent to oral CBZ? 3. Are the proposed dosing regimens acceptable? 4. Are the label statements acceptable?						
Other comments or information not included above	---						
Primary reviewer Signature and Date	Michael Bewernitz						
Secondary reviewer Signature and Date	Angela Yuxin Men						

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			Sponsor has provided results of bioequivalence assessment between the IV CBZ solution, IR CBZ, and ER CBZ.
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	The Agency agreed to a 505(b)(2) submission pathway.
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?		X		Define files are were not provided for the following datasets: cbz-auc-70-75-80.xls, cbzindparadose.xls, cbzpartial-aucsq4.xls, cbzsimconcq4.xls. An IR was sent to request define files for these studies.
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this	X			

	product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?				
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan status was granted.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION
FILEABLE? Yes**

A DSI inspection will be requested for the clinical and bioanalytical portions of study OV-1015.

The following comments were conveyed to the Sponsor in the 74-day letter:

1. Definition Files: Please provide a definition file for each of the following files:

- cbz-auc-70-75-80.xls*
- cbzindparadose.xls*
- cbzpartial-aucs4.xls*
- cbzsimconcq4.xls*

In each definition file, please include variable descriptions and, where applicable, units of measurement. In addition, please clarify the location of the simulated data representing the 75% and 80% oral dose conversion within the cbz-auc-70-75-80.xls file (only simulated data representing the 70% oral dose conversion data could be found). If the simulated data representing the 75% or 80% oral dose conversion were not included in the NDA submission, please submit them. Also, file cbzsimconcq4.xls appears to contain simulated concentrations for a single q4h IV infusion. Please re-submit cbzsimconcq4.xls with simulated concentrations for the full week of treatment (Day 1 to Day 7) for each subject using the corresponding q4h IV infusion regimen.

In addition, please include any relevant PK simulation parameters in the adpc.xpt dataset for study ov-1015-pauc (e.g., oral-to-IV dose conversion value, IV infusion interval [e.g., q4hr, q6hr], etc.) and resubmit this dataset.

*2. Project Files: Please submit Pharsight Phoenix project files (e.g., *.phxproj), input datasets, output datasets (e.g., individual simulated PK values) and any other files that are relevant to the IV infusion simulations. Also, please provide any scripts, spreadsheets, or other files relevant to the computation of any AUC values (for example, the partial AUC values) derived from the aforementioned simulated IV PK data.*

3. New Simulations: The PK simulation results shown in Figure 6 on page 13 in the OV-1015-MODSIM report demonstrate that the partial AUC 90% CI is expected to fall outside of the 80-125% range at various time points when switching to IV from oral IR q8hr carbamazepine. We recommend you conduct PK simulations to explore the feasibility of utilizing different dosing regimens and/or infusion parameters with a goal of producing an IV infusion concentration profile that meeting bioequivalence based on partial AUC after oral IR q8h carbamazepine and oral ER q12h

carbamazepine. We also recommend assessing the bioequivalence of C_{max} and C_{min} for this alternative IV infusion regimen in comparison with oral IR q8h carbamazepine as well as oral ER q12h carbamazepine.

It is possible the simulated PK data for the alternate IV infusion regimen may not achieve bioequivalence at every time point for the aforementioned exposure metrics for oral IR q8h and/or oral ER q12h carbamazepine. If so, and if you do not expect the alternate IV infusion regimen to result in a clinically significant worsening of efficacy or safety, please provide your justification.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Appendix 1: Tabular Listing of Clinical Studies

Type of Study	Study Identifier	Objectives(s) of the Study	Study Design & Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK and safety	OV-1015	1° - To assess the safety, tolerability, and PK of IV CBZ as a 30- and 15-minute infusion relative to orally administered CBZ in adult patients with epilepsy; and to compare the steady-state PK of intravenously administered CBZ (Day 7) relative to orally administered CBZ (Day 0). 2° - To assess the safety, tolerability, and PK of IV CBZ when administered over a 2- to 5-minute infusion in a subset of patients and to assess the safety, tolerability, and PK of IV CBZ in patients with mild or moderate renal impairment	Open Label	Carbamazepine Injection Total IV daily dose is converted at 70% of the total stable oral daily dose and administered in 4 divided doses every 6 hour over either 30-minute or 15-minute of infusions based on dosing cohorts enrolled. A subgroup of patients receiving 15-minute infusion also received for one additional day of IV carbamazepine infused over a period of 2 to 5 minutes <u>Route:</u> IV	Total: 98 55 patients in the 15 min infusion group 43 patients in the 30-min infusion group. A subset of 12 patients enrolled in the 15-min infusion group also received 2- to 5-min infusions	Patients diagnosed with any of the following: partial seizures with complex symptomatology (psychomotor, temporal lobe); Generalized tonic-clonic seizures (grand mal); mixed seizure patterns that includes one of the above or other partial or generalized seizures	7 days of IV CBZ administered Q6H for all cohorts except dosing cohorts 1C and 2C (2- to 5-minute infusions); 8 days of IV CBZ administered Q6H for dosing cohorts 1C and 2C	Completed; Full Report

Appendix 1: Tabular Listing of Clinical Studies (Continued)

Safety	13181A	1° - To assess the safety and tolerability of IV CBZ administered as multiple 15-minute infusions to adult patients with epilepsy on stable higher doses of oral carbamazepine. 2° - To assess the safety and tolerability of IV CBZ when administered as a 5-minute infusion; and to assess effect of IV CBZ on renal biomarkers	Open Label	Carbamazepine Injection Total IV daily dose is converted at 70% of total stable oral daily dose and administered in 4 divided doses in every 6 hour over a 15-minute infusion; the final infusion was a single 5-minute infusion, 6 hours after the last 15-minute infusion, at the dose previously administered as a 15-minute infusion <u>Route:</u> IV	Total : 105 All received 15 min fusion; 101 patients also received a one time 2-5min infusion .	Patients diagnosed with any of the following: partial seizures with complex symptomatology (psychomotor, temporal lobe); Generalized tonic-clonic seizures (grand mal); mixed seizure patterns that includes one of the above or other partial or generalized seizures	4 days of IV CBZ	Completed; Full report
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Appendix 2: Listing of PK Assay Reports

AEEL2: Validation report for carbamazepine and carbamazepine 10,11-epoxide (CBZ-E) analytical method

AEEO: Performance Report for carbamazepine and carbamazepine 10,11-epoxide (CBZ-E) analytical method

64743: Validation Report, LC-MS/MS detecting captisol in sodium heparin human plasma.

64731: Performance report, LC-MS/MS detecting captisol in sodium heparin human plasma.

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

/s/

MICHAEL A BEWERNITZ
06/25/2014

YUXIN MEN
06/25/2014