serum sodium 11 days later was 123mEq/L. He was asymptomatic and was discontinued from the study for hyponatremia. The sponsor reported that the final outcome was not known.
Subject *028E USA/M0945Y 561* was a 44YO female with anemia at baseline (attributed to dysfunctional uterine bleeding) but was allowed into the study. Early in the study she experienced increased seizure frequency, slow thinking, drowsiness and dizziness. Labs were drawn at this time and she was rolled over into the open label phase and given oxcarbazepine 1,200mg. Two days later, the lab result showed a serum sodium of 115mEq/L. She was called and had improvement in sensorium but was experiencing dyspnea. She was instructed to go to an emergency department for evaluation. Her serum sodium was 125mEq/L and hemoglobin was 8.4g/dL. She was admitted for correction of sodium and workup of dysfunctional uterine bleeding. Oxcarbazepine was discontinued.
Subject *04E USA/M8459P 106/506* was a 29YO male receiving oxcarbazepine 3,600mg/day. Thirty-five months after randomization he developed chest pain, weakness, and nausea and was admitted to a hospital to evaluate these symptoms. His serum sodium was 125mEq/L and had a "high" urine osmolality. Oxcarbazepine was tapered and he was treated with 3%NaCl. Three days later his serum sodium was 134mEq/L.
Subject *028E USA/M0587K 525* was a 60YO male who had 2 SAEs for hyponatremia. The first event occurred at the time he was hospitalized for a myocardial infarction. Two months after the MI, he experienced a seizure and dyspnea and was admitted. He had hyponatremia (not quantified) that was initially attributed to CHF and diuresis. During the hospitalization, oxcarbazepine dose was reduced from 3,000mg/day to 2,400mg/day and he was treated with fluid restriction, and demeclocycline. His serum sodium improved and he continued in the study.

The sponsor identified one oxcarbazepine patient *OT/E25 F/24/1094(93)* with an episode of renal colic (history of renal colic that predated oxcarbazepine exposure). There were no other serious AEs suggestive of nephrolithiasis or renal colic. There were no serious adverse events suggestive of renal failure or rhabdomyolysis.

4.8 Overall Discontinuations
Within the body of the ISS, the sponsor did not provide an overall summary of the reasons leading to dropout from oxcarbazepine trials. Instead, they provided a discussion of dropouts due to *AEs* within the ISS, and included information about the reasons for premature termination from studies in Appended Tables 6.4.1.-3 (overall), 6.4.2.-2 (adjunctive and monotherapy substitution trials) 6.4.3.-2 (initiation of monotherapy trials). These tables were not updated in the Safety Update. The sponsor did not provide a similar overall dropout summary for open label trials. The sponsor did not describe the administrative problems leading to discontinuation or if the patients that withdrew consent or were non-compliant had concomitant AEs. I have summarized the information from tables 6.4.2.-2 and 6.4.3.-2 below.

Reasons for Premature Termination By Treatment (Placebo controlled adjunctive therapy and monotherapy substitution trials)*

Reason for termination	Oxcarbazepine N=1,272		Carbamazepine N=134		Phenobarbital N=52		Placebo N=353	
	%	(n)	%	(n)	%	(n)	%	(n)
All Reasons	35.5%	(451)	35.1%	(47)	19.2%	(10)	17.3%	(61)
Adverse Event	21.9%	(278)	11.9%	(16)	5.8%	(3)	5.4%	(19)
Abnormal lab value	0.6%	(8)	5.2%	(7)	0	0	0.6%	(2)
Abnormal test procedure result	0.1%	(1)	0	0	0	0	0.3%	(1)
Unsatisfactory therapeutic effect	5.2%	(66)	10.4%	(14)	5.8%	(3)	5.4%	(19)
Patient no longer requires treatment	0.1%	(1)	0	0	0	0	0	0
Patient doesn't meet protocol criteria	1.7%	(22)	0	0	0	0	1.4%	(5)
Non compliance	1.4%	(18)	4.5%	(6)	0	0	1.1%	(4)
Withdrew consent	2.5%	(32)	2.2%	(3)	3.8%	(2)	1.4%	(5)
Loss to follow up	0.4%	(5)	0.7%	(1)	0	0	0.6%	(2)
Administrative problems	1.0%	(13)	0	0	3.8%	(2)	0.6%	(2)
Death	0.6%	(7)	0	0	0	0	0.6%	(2)

*From Table 6.4.2.-2, ISS

Reasons for Premature Termination by Treatment (Initiation of monotherapy trials)*

Reason for termination	Oxcarbazepine N=440		Phenytoin N=240		Valproic acid N=121		Placebo N=66	
	%	(n)	%	(n)	%	(n)	%	(n)
All Reasons	36.4%	(160)	39.6%	(95)	33.9%	(41)	22.7%	(15)
Adverse Event	9.1%	(40)	14.2%	(34)	9.9%	(12)	7.6%	(5)
Abnormal lab value	0.5%	(2)	0.4%	(1)	0.8%	(1)	1.5%	(1)
Unsatisfactory therapeutic effect	2.5%	(11)	1.7%	(4)	5.0%	(6)	0	0
Patient doesn't meet protocol criteria	6.4%	(28)	5.0%	(12)	2.5%	(3)	0	0
Non compliance	7.7%	(34)	6.3%	(15)	5.8%	(7)	1.5%	(1)
Withdrew consent	0.5%	(2)	0.4%	(1)	0	0	4.5%	(3)
Loss to follow up	5.0%	(22)	8.8%	(21)	5.8%	(7)	1.5%	(1)
Administrative problems	4.5%	(20)	2.1%	(5)	4.1%	(5)	6.1%	(4)
Death	0.2%	(1)	0.8%	(2)	0	0	0	0

*From Table 6.4.3.-2, ISS

These tables illustrate the differences in results for these study populations. While AEs were by far the most common reason leading to discontinuation from an adjunctive therapy or monotherapy substitution trial, AEs less frequently led to discontinuation from the initiation of monotherapy trials. In addition, although not explained, loss to follow up and administrative problems more frequently led to discontinuation for all treatment groups in the initiation of monotherapy trials.

In tables 6.4.2.-3 and 6.4.3.-3, the sponsor provided a description of the reasons leading to discontinuation by dose for the study groupings listed above. For the adjunctive therapy and monotherapy substitution trials (from Table 6.4.2.-3), AEs and unsatisfactory therapeutic effect appeared to demonstrate dose response relationships. For the monotherapy substitution trials, Patient non-compliance and Administrative Problems increased with increasing dose (see below).

Selected reasons leading to discontinuation by dose

Adjunctive therapy and monotherapy substitution trials

Reason	≤600mg (n=420)	>600-1200mg (n=619)	>1200-1800mg (n=373)	>1800mg (n=411)
Adverse event	9.5% (40)	13.4% (83)	11.8% (44)	27% (111)
Unsatisfactory therapeutic effect	1.9% (8)	2.3% (14)	4.0% (15)	7.1% (29)

Initiation of monotherapy trials

	≤600mg (n=108)	>600-1200mg (n=309)	>1200-1800mg (n=45)	>1800mg (n=4)
Non-compliance	5.6% (6)	7.1% (22)	13.3% (6)	0
Administrative problems	1.9% (2)	3.2% (10)	17.8% (8)	0

4.9 Discontinuations due to Adverse Events

The sponsor begins discussion of discontinuations due to AEs on p.166 of the ISS. The presentation followed the format of previously discussed safety presentations with regards to data pooling. The sponsor noted that reasons leading to discontinuations were recorded in 2 places within the case report form (termination page and/or the adverse event page of CRF, p.166 ISS). The sponsor reported that these 2 sources were not always congruent and therefore, depending on the source used, listings of the reasons leading to discontinuation may not agree (ISS p. 166).

4.9.1 Discontinuations due to AEs for all oxcarbazepine subjects, Primary Database

In the Safety Update, the sponsor reported that 19.7% (438/2,224) of oxcarbazepine exposed subjects discontinued from a trial due to AEs (pooled risk for RCTs and extensions). The following table from p.87 of the Safety Update summarizes the AEs leading to discontinuation of at least 1% of oxcarbazepine exposed epilepsy patients enrolled in trials.

Exhibit 6.4.1.-1. Adverse events causing premature discontinuation in 1% of patients (all OXC-treated patients with epilepsy)

	ISS	120-day
Adverse event	**n (%)**	**n (%)**
Number of patients	2191	2224
Number (%) of patients with premature discontinuation due to AEs	398 (18.2)	438 (19.7)
Nervous system	274 (12.5)	295 (13.3)
Dizziness	102 (4.7)	106 (4.8)
Ataxia	86 (3.9)	89 (4.0)
Somnolence	69 (3.1)	71 (3.2)
Headache	47 (2.1)	52 (2.3)
Nystagmus	45 (2.1)	46 (21)
Abnormal gait	28 (1.3)	28 (1.3)
Tremor	24 (1.1)	27 (1.2)
Digestive system	146 (6.7)	154 (6.9)
Vomiting	85 (3.9)	89 (4.0)
Nausea	82 (3.7)	82 (3.7)
Special senses	139 (6.3)	142 (6.4)
Diplopia	89 (4.1)	92 (4.1)
Vertigo	36 (1.6)	36 (1.6)
Abnormal Vision	33 (1.5)	33 (1.5)
Body as a whole	64 (2.9)	68 (3.1)
Fatigue	37 (1.7)	39 (1.8)
Skin and appendages	57 (2.6)	66 (3.0)
Rash	31 (1.4)	39 (1.8)

Source: 120-day Table 6.4.1.-2 and ISS Table 6.4.1.-2

In addition to the common events leading to discontinuation listed above, 1 subject discontinued for hepatitis (OT/PE1 I/6/686 see above), 1 for hepatic function abnormal (010 600 GB/5 1041/22-increased LDH, ALP), and 2 for transaminase elevations (see lab section). Three discontinued for leucopenia, 1 for granulocytopenia, 14 for hyponatremia, and 1 for renal calculus. There were no discontinuations for aplastic anemia, renal failure, or rhabdomyolysis.

4.9.2 Discontinuations due to AEs from Controlled Trials, Primary Database
Discontinuations due to AEs from adjunctive therapy and monotherapy substitution trials
Almost 22% (278/1,272) of the oxcarbazepine exposed subjects enrolled in these trials discontinued for adverse events (compared to 5.4% of placebo subjects, 11.9% of carbamazepine subjects, and 5.8% of phenobarbital subjects). The sponsor also reported that the overall risk for discontinuation for AE among oxcarbazepine subjects appeared dose related (≤600mg/day: 9.5%, >600-1,200mg/day: 13%, >1,200-1,800mg/day: 12%, and ≥1,800mg/day: 27%). In study OT/PE1, the intended highest dose at commencement of the trial was 2,400mg/day. The investigators observed a high discontinuation due to AE rate (34%) in the 2,400mg/day dose group and as a result the protocol was amended to reduce the highest dose to 1,800mg/day (Protocol OT/PE1, Amendment 2, p.11).

I used sponsor's table 6.4.2.-1 to identify the AEs leading to dropout that occurred in at least 1% of those exposed to oxcarbazepine and that had a relative risk of at least 2 when compared to any of the alternatives (placebo, carbamazepine, or phenobarbital). The observed risks for those events leading to discontinuation are summarized in the following table.

Selected AEs Leading to Discontinuation from Adjunctive Therapy and Monotherapy Substitution Trials

Event	Oxcarbazepine n=1,272		Placebo n=353		Carbamazepine N=134		Phenobarbital n=52	
	%	n	%	n	%	n	%	n
Nausea	5.4	69	0.8	3	0.7	1	0	0
Vomiting	6.1	78	0.3	1	1.5	2	1.9	1
Ataxia	6.3	80	1.1	4	0.7	1	0	0
Dizziness	6.8	87	1.4	5	2.2	3	0	0
Gait abnormal	2.1	27	0.3	1	0	0	0	0
Headache	2.9	37	0.3	1	1.5	2	0	0
Nystagmus	3.4	43	0.8	3	0	0	0	0
Tremor	1.9	24	0.6	2	0	0	0	0
Diplopia	6.2	79	0.6	2	0	0	0	0
Vertigo	2.8	35	0	0	0	0	0	0
Vision abnormal	2.4	30	0.3	1	0	0	0	0
Rash (rash, rash erythem and rash maculopap)	1.7	23	0	0	2.2	3	1.9	1

The sponsor did not provide an analysis of discontinuation due to specific AEs by dose for this grouping of the data. I reviewed the study report for study OT/PE1 a large adjunctive therapy controlled trial. Exhibit 9.2.-2 on p.812 of this study report provided the discontinuation due to AE risk for specific events by dose. Exhibit 9.2.-2 demonstrated a dose response for discontinuation for all of the events in the above table except rash.

Discontinuations due to AEs from Initiation of Monotherapy Trials
The sponsor reported that 9.1% (40/440) of the oxcarbazepine exposed subjects in these trials discontinued for AEs (compared to 7.6% receiving placebo, 14.2% receiving phenytoin, and 9.9% receiving valproic acid). There did not appear to be an overall discontinuation for AE dose response relationship in these studies. The sponsor reported that rash, dizziness, and nausea were the only AEs leading to premature discontinuation in more than 1% of oxcarbazepine patients. The following table includes the AEs leading to dropout that occurred in at least 1% of those exposed to oxcarbazepine and that had a relative risk of at least 2 when compared to placebo, phenytoin, or valproic acid.

Selected AEs Leading to Discontinuation from Initiation of Monotherapy Trials

Event	Oxcarbazepine n=440		Placebo n=66		Phenytoin N=240		Valproic acid n=121	
	%	n	%	n	%	n	%	n
Nausea	1.1.	5	1.5	1	0	0	1.7	2
Rash (rash, rash erythem and rash maculopap)	2.3	10	0	0	5.0	12	0	0

4.9.3 Discontinuations from the Mania Trial
Four subjects discontinued from mania studies (Subject 10/505 vomiting, abdominal pain; Subject 2/502 rash; Subject 11/506 limb weakness, diplopia, dizziness, dysphoria; Subject 26/514 ataxia, dizziness, vomiting, and headache).

The sponsor provided no separate summary of information addressing dropouts due to AEs from long-term extension trials or open label studies.

4.10 Treatment Emergent Adverse Events
The sponsor's approach to describing treatment emergent adverse events was to make separate presentations for the overall primary database (epilepsy patients), the adjunctive therapy and monotherapy substitution trials, and the initiation of monotherapy trials, the mania trial and the trial with hepatically impaired subjects. There was no separate presentation of AEs for the extension trials. The sponsor provided tables describing the occurrence of AEs by body systems and for the occurrence of each specific AE.

4.10.1 Adverse Events for all Oxcarbazepine Exposed, Primary Database
In sponsors' Exhibit 5.2.1.-2 from p. 47 of the Safety Update, they provided a summary of the most commonly reported (in at least 10%) adverse events for the oxcarbazepine exposed epilepsy patients in the primary database. That table is provided below.

Exhibit 5.2.1.-2. Common adverse events (those that occurred in at least 10% of patients) regardless of relationship to trial drug by preferred term in descending order of frequency in the 120-day Safety Update (all OXC-treated patients with epilepsy)

	ISS		120-day	
Preferred term[1]	N	%	N	%
Total patients	2191	100.0	2224	100.0
Total patients with adverse events	1863	85.0	1942	87.3
Headache	666	30.4	723	32.5
Dizziness	569	26.0	636	28.6
Somnolence	543	24.8	588	26.4
Nausea	394	18.0	442	19.9
Vomiting	350	16.0	397	17.9
Diplopia	324	14.8	360	16.2
Infection viral	298	13.6	343	15.4
Fatigue	294	13.4	334	15.0
Ataxia	210	9.6	255	11.5
Vision abnormal	188	8.6	225	10.1
Pain abdominal	193	8.8	224	10.1

Source: ISS Table 5.2.1.-2; 120-day Table 5.2.1.-2
[1] A patient with multiple occurrences of the same adverse event is counted only once in each category.

4.10.2 Adverse Events Controlled Trials, Primary Database

The sponsor's presentation of AE data from the adjunctive therapy and monotherapy substitution trials and the initiation of monotherapy trials allowed comparison of adverse event occurrence by treatment and by dose for oxcarbazepine. Sponsor's tables 5.2.2.-4 and 5.2.3.-4 provided the percentage of subjects by treatment that experienced each AE for the adjunctive therapy and monotherapy substitution trials and the initiation of monotherapy trials, respectively. Sponsor's tables 5.2.2.-5 and 5.2.3.-5 provided the percentage of oxcarbazepine subjects reporting each AE by dose. Using these tables, I identified the AEs occurring in at least 1% of oxcarbazepine subjects and that occurred at least 2 times more frequently than in the placebo group. I then reviewed these tables and identified those events where the percentage with the AE in the highest dose group was higher than the lower dose groups (suggesting a dose response). I included only those events reported by at least 5% in the highest dose group. In addition, I included the percentage of patients reporting AEs in the active comparator groups. For the adjunctive therapy and monotherapy substitution trials, I report the dose groups that the sponsor used. For the initiation of monotherapy trials, I combined the sponsor's upper two dose groups (>1,200-1,800mg and >1,800mg) into one category since the highest dose group contained only 3 subjects.

Selected Adverse Events from Adjunctive Therapy and Monotherapy Substitution Trials*

	Oxcarbazepine Mean Daily Dose				Placebo	Carbamazepine	Phenobarbital
Adverse Event	≤600mg (n=251)	>600-1200mg (n=441)	>1200-1800mg (n=204)	>1800mg (n=376)	(n=353)	(n=134)	(n=52)
Dizziness	20.7% (52)	20% (88)	25.5% (52)	35.6% (134)	10.8% (38)	13.4% (18)	3.8% (2)
Nausea	15.9% (40)	14.7% (65)	17.6% (36)	24.2% (91)	7.4% (26)	10.4% (14)	5.8% (3)
Diplopia	11.2% (28)	15% (66)	18.6% (38)	23.1% (87)	2.5% (9)	2.2% (3)	0
Vomiting	15.1% (38)	16.1% (71)	15.2% (31)	19.9% (75)	8.2% (29)	3% (4)	3.8% (2)
Ataxia	7.6% (19)	9.3% (41)	14.7% (30)	14.6% (55)	4.2% (15)	4.5% (6)	1.9% (1)
Vision abnormal	5.2% (13)	8.4% (37)	11.8% (24)	12.8% (48)	2.5% (9)	4.5% (6)	0
Vertigo	4.4% (11)	6.3% (28)	7.4% (15)	8% (30)	1.4% (5)	0.7% (1)	11.5% (6)
Dyspepsia	4.4% (11)	3.4% (15)	2.9% (6)	8% (30)	1.7% (6)	3.7% (5)	1.9% (1)

*From ISS Tables 5.2.2.-4 and 5.2.2.-5

Selected Adverse Events from Initiation of Monotherapy Trials*

	Oxcarbazepine Mean Daily Dose			Placebo	Phenytoin	Valproic acid
Adverse Event	≤600mg (n=96)	>600-1200mg (n=297)	>1200mg (n=47)	(n=66)	(n=240)	(n=121)
Headache	30.2% (29)	38% (113)	48.9% (23)	12.1% (8)	50% (120)	33.1% (40)
Somnolence	14.6% (14)	21.9% (65)	34% (16)	6.1% (4)	30.4% (73)	19.8% (24)
Dizziness	11.5% (11)	20.5% (61)	29.8% (14)	4.5% (3)	24.6% (59)	15.7% (19)
Diarrhea	6.3% (6)	5.4% (16)	8.5% (4)	1.5% (1)	5% (12)	8.3% (10)
Apathy	5.2% (5)	4.7% (14)	10.6% (5)	1.5% (1)	6.7% (16)	0
Weight increased	0	5.1% (15)	8.5% (4)	1.5% (1)	0.4% (1)	21.5% (26)
Arthralgia	2.1% (2)	3.4% (10)	8.5% (4)	1.5% (1)	1.7% (4)	0.8% (1)
Acne	2.1% (2)	3.4% (10)	6.4% (3)	0	5.4% (13)	1.7% (2)
Tremor	3.1% (3)	2% (6)	12.8% (6)	0	7.5% (18)	17.4% (21)
Alopecia	0	3.4% (10)	8.5% (4)	0	1.2% (3)	19% (23)
Trauma	0	1.3% (4)	6.4% (3)	0	2.5% (6)	0.8% (1)

* From ISS Tables 5.2.3.-4 and 5.2.3.-5

These tables demonstrate that, with the exception of infection viral and fatigue, the common events identified for the all oxcarbazepine exposed grouping occurred at least twice as frequently in oxcarbazepine subjects compared to placebo subjects in RCT databases and the data suggested dose response relationships for these events. In addition, there were several AEs that demonstrated a dose response relationship but that did not meet the cutoff (at least twice as common compared to control). Those events included fatigue, insomnia, nervousness, and anxiety.

I reviewed both the sponsor's AE data set (ADV.xpt) as well as table 5.2.1.-1 from the Safety Update to identify uncommon specific events of interest. In addition to the serious hepatic events and hepatic events leading to discontinuation discussed above, there were 2 oxcarbazepine exposed subjects with events described as jaundice and 7 with transaminase elevations (see review of systems). Four oxcarbazepine subjects developed granulocytopenia and 15 developed leukopenia. There were no adverse events in oxcarbazepine exposed subjects suggestive of Stevens Johnson syndrome, toxic epidermal necrolysis, or rhabdomyolysis.

4.10.2.1 Adverse Events by Age

The sponsor suggests in labeling that there is no difference in the safety when comparing children to adults. Their approach to exploring age/AE relationships was to examine AE risks for the entire oxcarbazepine exposed population stratified by age group with no comparator group (Safety Update, p56). Using this approach, it would not be possible to evaluate differences between ages that reflected the background differences in risk, regardless of drug exposure. To look for differences in AE risk by age, I requested SAE, discontinuation due to AE and AE tables from the sponsor for the adjunctive therapy/monotherapy substitution trials and the initiation of monotherapy trials by treatment and stratified by age groups. I intended to calculate relative risks for each age group and then compare the relative risks across age strata to look for drug/age interactions.

The following table illustrates the number of individuals exposed in controlled trials stratified by age.

Number exposed by age group, Adjunctive therapy/Monotherapy substitution trials

Age group	Oxcarbazepine	Placebo	Active Comparator
<6 years old	14	16	0
6-11 years old	59	51	0
12-17 years old	99	72	3
18-64 years old	1082	213	153
>=65 years old	18	1	10

Number exposed by age group, Initiation of Monotherapy trials

Age group	Oxcarbazepine	Placebo	Active Comparator
<6 years old	7	2	0
6-11 years old	66	9	60
12-17 years old	72	6	67
18-64 years old	263	30	232
>=65 years old	32	19	1

There were too few individuals in the youngest age groups and too few events to allow for meaningful comparisons of SAE and discontinuation due to AE relative risks across age groups. For the common AEs, I examined the relative risks from the adjunctive therapy/monotherapy substitution trials to look for evidence of differences in relative risk across age groups. With few patients in the extreme age groups (<6, ≥65) I combined the data for these patients with the

adjacent age groups and calculated relative risks based on the pooled experience. The results of that analysis are included in the following table.

Comparison of Common AE risks by age for the Adjunctive Therapy/Monotherapy Substitution Trials

	≤11 years old			12 to 17 years old			≥18 years old		
	Oxc	PBO	RR	Oxc	PBO	RR	Oxc	PBO	RR
	n=73	n=67		n=99	n=72		n=1100	n=214	
Event									
Fatigue	9.5%	8.9%	1.1	15%	8.3%	1.8	14.2%	5.6%	2.5
Vomiting	32.8%	19.4%	1.7	33%	8.3%	4.0	14.8%	4.7%	3.2
Hyponatremia	1.4%	0	-	1%	0	-	3.5%	0.4%	7.4
Ataxia	13.7%	7.5%	1.8	13%	1.4%	9.3	11.4%	4.2%	2.7
Dizziness	21.9%	10.4%	2.1	32%	5.6%	5.7	27.2%	12.6%	2.2
Emot lability	6.8%	1.5%	4.5	9%	5.6%	1.6	1.9%	0.9%	2.0
Headache	34.2%	16.4%	2.1	28%	22%	1.3	28.5%	21.9%	1.3
Nervousness	4.1%	7.4%	0.6	5%	2.8%	1.8	3.2%	0.9%	3.4
Somnolence	32.8%	16.4%	2.0	29%	9.7%	3.0	25.8%	9.3%	2.8
Rash*	5.5%	7.5%	0.7	8%	4.2%	1.9	5.9%	1.9%	3.2
Diplopia	19.2%	1.5%	12.8	16%	0	-	18%	3.7%	4.8
Vision abnl	11%	1.5%	7.3	15%	1.4%	10.7	9.4%	3.2%	2.9

* Combines the preferred terms rash, rash erythematous, and rash maculopapular

The relative risks were highest in the oldest age group for fatigue, vomiting, hyponatremia, nervousness, and rash. The youngest age group had the highest relative risks for emotional lability, diplopia and headache.

4.10.2.2 Adverse Events by Gender

To look for drug/gender interactions, the sponsor reported AE risk for the entire population stratified by gender, without a comparator group. For my evaluation, I used the drug/gender AE table from the study report for study OT/PE1 an adjunctive therapy, placebo control trial. In this trial, there were 264 males exposed to oxcarbazepine and 77 exposed to placebo and there were 255 females exposed to oxcarbazepine and 96 exposed to placebo. I calculated, and then compared relative risks for males and females for common AEs. For dyspepsia, nausea, abdominal pain, coordination abnormal, and dizziness, the relative risks when comparing to placebo were greater than one and were similar for males and females. The following table summarizes selected AEs where there was at least a two-fold difference for relative risks when comparing genders.

Selected Adverse Event Risks and Relative Risks Stratified by Gender, Study OT/PE1

Adverse Event	OXC male	Placebo Male	OXC female	Placebo female	RR male	RR female
Fatigue	12.5% (33)	9% (7)	15.2% (39)	5.2% (5)	1.4	2.9
Fever	3.8% (10)	1.3% (1)	3.1% (8)	5.2% (5)	2.9	0.6
Anorexia	1.5% (4)	2.6% (2)	2.7% (7)	2.1% (2)	0.6	1.3
Constipation	3.4% (9)	2.6% (2)	3.1% (8)	5.2% (5)	1.3	0.6
Vomiting	20.8% (55)	1.3% (1)	27.1% (69)	7.3% (7)	16.0	3.7
Amnesia	2.2% (6)	1.3% (1)	1.0% (2)	3.1% (3)	1.8	0.3
Ataxia	18.6% (49)	7.8% (6)	21.2% (54)	3.1% (3)	2.4	6.8
Insomnia	3.8% (10)	1.3% (1)	2.0% (5)	2.1% (2)	2.9	0.9
Vision abnl	8.0% (21)	3.9% (3)	17.3% (44)	4.2% (4)	2.0	4.1

The data from this study suggest differences in risk by gender for these events. Additional studies would be necessary to confirm drug/gender interactions.

4.10.3 Plasma concentration/AE relationships
The sponsor explored the relationship between C_{min} for MHD and AEs in 4 protocols (011, 025, 026, and OT/PE1). C_{min} for MHD was measured directly in OT/PE1 (trough levels) and was estimated using random serum concentrations (by modeling) for the remaining studies. The sponsor focused on AEs occurring in at least 10% of one of the oxcarbazepine treatment groups. In protocols 025 and 026, dizziness, headache, and nausea met the 10% cutoff but only dizziness exhibited a significant association with C_{min} for MHD. In study 011, ataxia, diplopia, dizziness, headache, nausea, somnolence, and vomiting met the 10% occurrence criteria and all seven events were significantly associated with C_{min} for MHD. In protocol OT/PE1, the same seven events listed for study 011 met the 10% cutoff and all but headache and nausea were significantly associated with C_{min} for MHD.

4.11 Laboratory Evaluation
The protocols for the studies included in the ISS required laboratory monitoring. In general, the required tests included hematology, blood chemistry, and urinalysis (in 5 studies urinalysis was not performed and in 1 study, hematology testing was not performed). In addition, in 8 trials, thyroid tests were performed. The ISS did not comment on the specifics of testing. I reviewed several of the study protocols and there was no uniform requirement for the use of a central lab. The protocol of a OT/PE 1, a multi-center/multi-national study, included the comment that only quality checked clinical laboratories will be used, preferably central laboratory in each country (p. 27 Clinical Trial Report for OT/PE 1). In study 004, the baseline lab tests were analyzed locally while the end study tests were sent to a central lab.

On p. 169 of the ISS, the sponsor begins a discussion of laboratory results from the oxcarbazepine development program. In the opening paragraph of this section, the sponsor states that lab data had been pooled and presented for three different groupings; all oxcarbazepine epilepsy subjects, adjunctive therapy and monotherapy substitution trial subjects and monotherapy initiation trial subjects. All of the collected lab data were summarized for the all oxcarbazepine grouping in the body of the ISS but the sponsor selected the lab parameters that were summarized in the body of the ISS for the other two groupings (complete tables were provided in appendices).

Because I had concerns about the validity of analyses performed on the data pooled from different studies, I conducted additional analyses from a single study. Study OT/PE1 included over 500 subjects exposed to oxcarbazepine and over 150 subjects to placebo (added to other therapies). Using the lab data from this trial that was submitted with the NDA, I performed mean change from baseline analyses and outlier analyses. For the mean change from baseline analyses, I selected patients who had normal results at baseline and calculated the change from baseline for the final on drug result (visit 4 or later) for given parameters. For the outlier analyses, I selected subjects with normal baseline results that crossed selected outlier thresholds.

In their overall summary of lab changes (p. 170, ISS) the sponsor identified 3 parameters that appeared to change with exposure to oxcarbazepine. The sponsor describes decreases in serum sodium, T_4, and uric acid. They state the T_4 changes did not appear to be dose related but may be related to increased duration of exposure and proposed a protein binding mechanism. In addition, they noted that TSH and T_3 did not change. They state that the decreases in uric acid and serum sodium did appear to show a dose response relationship.

4.11.1 Mean change from baseline
4.11.1.1 All Oxcarbazepine Exposed, Primary Database
The sponsor presented tables summarizing the mean changes from baseline by dose and duration of exposure for this grouping. These tables are included as attachments. The sponsor interpreted

these data as demonstrating decreases in mean T_4 across all dosing groups that were not clinically relevant, and without changes in T_3 or TSH. The sponsor reported that the data described decreases in serum uric acid that are more pronounced with increasing doses of oxcarbazepine and that are unlikely to be clinically significant. The sponsor also stated that the data describes decreases in serum sodium that are more pronounced with increasing oxcarbazepine doses and that appear stable over time. In the following table, I present the sponsor's analyses of these lab parameters.

Mean change from baseline for sodium, uric acid and T_4, all oxcarbazepine treated subjects from in text table 7.1.1.-1.

	≤600mg/day			>600-1200mg/day			>1200-1800mg/day			>1800mg/day			All doses		
	N	meanΔ	SD	N	meanΔ	SD	N	meanΔ	SD	N	meanΔ	SD	N	meanΔ	SD
Sodium (mmol/L)															
≤ 1 mo.	187	-1.13	5.16	445	-1.30	4.58	222	-1.65	4.24	254	-1.54	5.13	1108	-1.39	4.75
>1-3 mo.	189	-0.63	3.97	756	-1.01	7.00	299	-1.42	4.56	347	-1.60	5.02	1591	-1.17	5.88
>3-6 mo.	117	-2.26	4.74	455	-0.99	4.46	231	-1.13	4.55	279	-1.88	4.84	1082	-1.39	4.63
>6-12 mo.	118	-1.04	5.31	540	-1.37	8.01	215	-2.13	4.96	233	-1.99	5.45	1106	-1.61	6.74
>12-24 mo.	54	-1.15	5.79	395	-1.47	8.96	161	-1.88	5.34	151	-1.90	5.69	761	-1.62	7.51
>24-36 mo.	28	0.86	5.32	167	-1.11	12.61	29	-2.67	4.21	24	0.93	0.01	248	-0.87	10.98
Uric acid (µmol/L)															
≤ 1 mo.	141	-6.76	38.89	338	-19.62	50.56	186	-27.38	58.20	222	-37.48	65.11	887	-23.67	55.48
>1-3 mo.	112	-7.08	48.97	309	-20.40	53.74	194	-19.58	65.18	273	-43.91	82.02	888	-25.77	66.74
>3-6 mo.	82	-6.54	44.26	291	-16.26	58.17	173	-15.98	69.77	231	-38.66	86.59	777	-21.83	69.99
>6-12 mo.	61	3.90	63.64	202	-20.16	59.73	127	-16.58	71.75	171	-50.80	94.14	561	-26.07	76.69
>12-24 mo.	11	-12.65	74.03	110	-28.50	68.00	89	-23.12	60.12	104	-52.68	76.89	314	-34.43	70.16
>24-36 mo.	1	47.58	0.00	3	-49.55	49.85	2	-44.61	88.32	12	-82.28	97.14	18	-65.42	88.90
T_4 (nmol/L)															
≤ 1 mo.	105	-3.88	16.68	313	-7.80	16.85	118	-6.70	15.63	163	-3.85	25.77	699	-6.10	19.15
>1-3 mo.	124	-7.41	20.56	440	-11.61	24.76	165	-10.05	19.48	259	-8.80	22.73	988	-10.08	22.93
>3-6 mo.	80	-4.81	16.21	273	-11.13	20.13	128	-11.26	18.20	211	-10.67	20.53	692	-10.28	19.56
>6-12 mo.	92	-9.51	19.95	349	-14.48	22.93	137	-13.99	23.75	190	-14.42	23.85	768	-13.78	22.99
>12-24 mo.	46	-22.35	27.42	245	-12.49	60.70	103	-14.20	23.27	122	-18.77	25.76	516	-15.19	45.67
>24-36 mo.	24	-31.14	22.77	111	-24.90	29.84	18	-27.40	27.41	19	-29.85	35.74	172	-26.58	29.28

Interpretation of the sponsor's mean change from baseline analysis for the all exposed group is somewhat difficult. This analysis lacks information from a comparator group. The sponsor's tables result from pooling of trials in different populations and from studies with different designs and monitoring schedules. The presentation is stratified by time and it is unclear if those subjects exposed for longer periods are similar to those exposed for shorter periods. In addition, it is possible that some of those dropping out did so for reasons related to the lab parameter being examined. With that said, except for the parameters included in the above table, there did not appear to be any consistent time or dose related changes for the remaining laboratory test results.

4.11.1.2 Controlled Trials, Primary Database

Mean change from baseline for Adjunctive and monotherapy substitution trials

In summarizing the lab data for this grouping, the sponsor felt the data suggested that there was a slight decrease in TSH but noted that there were no placebo group data for comparison. In addition they found decreases in T_4 (not dose related) and no change in T_3. They concluded that the observed changes in TFTs did not appear to be significant. They observed decreases in uric acid in the oxcarbazepine group (dose related) and increases in the placebo group. They also described decreases in sodium (suggesting a dose relationship) in the oxcarbazepine group that they described as stable over time, with no change in the placebo group.

Monotherapy initiation trials

As in the previous analyses, the evidence suggested that oxcarbazepine exposure was associated with decreases in mean sodium, T_4 and uric acid. There were fewer patients in these analyses than in the previous analyses.

Study OT/PE1

The following table summarizes the results from the mean change from baseline analysis for chemistry lab data from study OT/PE1.

Mean change from baseline for chemistry lab parameters, Study OT/PE1

Analyte (units)	Oxcarbazepine Mean change from baseline (n)	Placebo Mean change From baseline (n)
SGOT (U/L)	0.99 (491)	0.61 (101)
SGPT (U/L)	0.92 (487)	0.13 (101)
Total Bilirubin (µmol/L)	-0.29 (503)	0.06 (104)
GGT (U/L)	5.09 (174)	1.37 (41)
LDH (U/L)	11.40 (411)	12.29 (92)
Creatinine (µmol/L)	0.70 (498)	0.04 (104)
BUN (mmol/L)	-0.02 (489)	0.16 (101)
Sodium (mmol/L)	-0.51 (450)	0.64 (90)
Potassium (mmol/L)	0.04 (466)	0.03 (99)
Bicarbonate (mmol/L)	0.14 (361)	0.18 (74)
Chloride (mEq/L)	-0.80 (446)	0.15 (88)
Thyroxine (nmol/L)	-7.62 (406)	-0.99 (82)

In general, the mean changes from baseline tended to be small and in the same direction for oxcarbazepine and placebo. The findings for thyroxine and sodium were consistent with the findings previously presented by the sponsor.

The following table summarizes the results from the mean change from baseline analysis for hematology lab data from study OT/PE1.

Mean change from baseline for hematology lab parameters, Study OT/PE1

Analyte (units)	Oxcarbazepine Mean change from baseline (n)	Placebo Mean change from baseline (n)
Hemoglobin (g/dL)	-0.12 (413)	-0.12 (83)
Hematocrit (%)	-0.13 (430)	0.47 (86)
Platelet count (10^9/L)	12.68 (458)	-4.39 (96)
White blood cell count (10^9/L)	-0.12 (451)	-0.23 (94)
ANC* (10^9/L)	-0.20 (441)	-0.19 (91)

*ANC, absolute neutrophil count, calculated by multiplying the %neutrophilsxWBCs, analysis includes those with a baseline ANC≥2000

With the exception of platelet count, the changes were similar for oxcarbazepine and placebo.

4.11.2 Outlier analyses

The sponsor provided a discussion of treatment emergent laboratory abnormalities. They defined these as lab values that were normal at baseline and above or below a specified range (local laboratory defined) during treatment. Again, the sponsor grouped the data into all oxcarbazepine treated patients, adjunctive and monotherapy substitution trials, and monotherapy initiation trials. For these outlier analyses, the sponsor classified the events by the mean daily dose of drug received.

4.11.2.1 All Oxcarbazepine Exposed Subjects, Primary Database

For T_4, the outlier risk for those with a normal baseline value was 11.1% and there appeared to be evidence of a dose response relationship. For uric acid, 22.9% of oxcarbazepine patients went from normal to abnormally low and there also appeared to be evidence of a dose response relationship. For sodium, 9.1% of those with normal baseline became abnormally low (<135mmol/L) but there did not appear to be a dose response relationship.

4.11.2.2 Controlled Trials, Primary Database

Outlier Analysis Adjunctive Therapy/Monotherapy Substitution Trials

The sponsor provided tables which depicted the %/number of individuals who had outliers and baseline and those with outliers on their final measurement for oxcarbazepine and placebo. I summarized the results in the following table.

Adjunctive therapy/Monotherapy substitution trial selected chemistry lab outliers from sponsor's table 7.2.2.-3

	Oxcarbazepine		Placebo	
Analyte (criteria)	% at baseline	% during study	% at baseline	% during study
Tbili (>43µmol/L)	(0/1115)	0.2% (2/1084)	(0/346)	0.6% (2/348)
AST (>100U/L)	0.3% (4/1227)	0.8% (10/1203)	(0/347)	(0/347)
ALT (>110U/L)	0.3% (4/1226)	0.2% (3/1204)	0.3% (1/347)	0.9% (3/347)
Alk Phos (>280U/L)	10.8% (120/917)	13.1% (142/886)	15%(52/347)	19.5%(68/348)
BUN (>14.3mmol/L)	0.1% (1/1115)	(0/1084)	(0/313)	(0/310)
Chloride(<85mmol/L)	0.1% (1/1157)	0.8% (9/1156)	(0/345)	0.6%(2/348)
Creatinine(>221µmol/L)	0.1% (1/1229)	0.3% (4/1202)	(0/347)	(0/347)
GGT (>ULN)	57% (437/770)	62% (464/747)	60%(102/327)	66.7%(114/339)
LDH (>500U/L)	3.6%(25/687)	7.9%(52/658)	2.9%(10/344)	5.5%(19/348)
Sodium (<125mmol/L)	(0/1227)	3.2%(38/1203)	(0/347)	(0/346)
TSH (>ULN)	2.7%(5/48)	2.1%(4/43)	2.1% (1/48)	2.1%(1/48)
T_3(<LLN)	7.9%(53/668)	20.7%(135/653)	7.2%(14/195)	22.8%(46/202)
T_4(<LLN)	12.1%(96/791)	30.2%(239/792)	13.7%(29/211)	20%(44/220)
Uric Acid(<89µmol/L)	0.2%(2/949)	5.5%(51/922)	0.9%(3/342)	2.3%(8/348)

Adjunctive therapy/Monotherapy substitution trial selected hematology lab outliers from sponsor's table 7.2.2.-3

	Oxcarbazepine		Placebo	
Analyte (criteria)	% at baseline	% during study	% at baseline	% during study
Hematocrit (<30%)	0.2%(2/1039)	0.8%(8/1004)	0.6%(2/347)	1.2%(4/346)
Hemoglobin (<100g/L)	0.5%(6/1237)	1.6%(19/1201)	0.9%(3/347)	1.7%(6/346)
WBC (<3.0)	0.7%(8/1237)	2.3%(28/1201)	0.9%(3/347)	2.9%(10/346)
Neutrophils (<LLN)	8.5% (69/811)	14.5% (113/782)	11.2%(19/169)	24.2%(41/169)
Platelet (<100)	0.3%(3/1224)	0.9%(11/1194)	(0/346)	1.2%(4/345)

The chemistry table suggests that for sodium and T_4 there were similar percentages of outliers between treatment groups at baseline but a higher percentage of outliers on oxcarbazepine during the study. The hematology outlier table did not appear to demonstrate substantial differences in risk between treatment groups.

Outlier Analysis Initiation of Monotherapy trials
An analysis of outliers similar to the one presented above was provided for the initiation of monotherapy trials. I summarized that information below.

Initiation of Monotherapy trial selected chemistry lab outliers from sponsor's table 7.2.3.-3

	Oxcarbazepine		Placebo	
Analyte (criteria)	% at baseline	% during study	% at baseline	% during study
Tbili (>43µmol/L)	(0/428)	0.5%(2/405)	(0/63)	(0/63)
AST (>100U/L)	0.2%(1/426)	1%(4/405)	(0/63)	(0/63)
ALT (>110U/L)	1.2%(5/423)	1.2%(5/406)	(0/63)	(0/63)
Alk Phos (>280U/L)	14.8%(63/427)	22.3%(90/404)	23.8%(15/63)	25.4%(16/63)
BUN (>14.3mmol/L)	(0/70)	(0/65)	(0/63)	(0/63)
Chloride(<85mmol/L)	(0/411)	0.8%(3/402)	(0/63)	(0/63)
Creatinine(>221µmol/L)	(0/413)	0.3%(1/401)	(0/63)	(0/63)
LDH (>500U/L)	2.6%(1/38)	8.8%(3/34)	(0/20)	(0/29)
Sodium (<125mmol/L)	(0/423)	1%(4/406)	(0/64)	(0/63)
TSH (>ULN)	4.9%(3/61)	4.2%(2/48)	2%(1/49)	2.2%(1/46)
T_3(<LLN)	6.6%(4/61)	8.3%(4/48)	3.9%(2/49)	2.2%(1/46)
T_4(<LLN)	0.9%(3/353)	6.6%(22/336)	4%(2/50)	2.2%(1/46)
Uric Acid(<89µmol/L)	(0/32)	3.2%(1/31)	2.9%(1/35)	5.9%(2/34)

Initiation of Monotherapy trial selected hematology lab outliers from sponsor's table 7.2.2.-3

	Oxcarbazepine		Placebo	
Analyte (criteria)	% at baseline	% during study	% at baseline	% during study
Hematocrit (<30%)	(0/67)	(0/65)	(0/62)	1.6%(1/63)
Hemoglobin (<100g/L)	0.7%(3/409)	0.5%(2/407)	(0/62)	1.6%(1/63)
WBC (<3.0)	0.5%(2/408)	1.5%(6/407)	(0/62)	1.6%(1/63)
Neutrophils (<LLN)	2%(7/350)	6.4%(22/357)	4.4%(1/23)	8%(2/25)
Platelet (<100)	0.3%(1/406)	0.3%(1/357)	1.6%(1/62)	(0/63)

When compared to the outlier analyses for the adjunctive therapy/monotherapy substitution trials, the results from these analyses demonstrated lower percentages of outliers.

Outlier analysis for Study OT/PE1
As mentioned above, I conducted additional analyses using the sponsor's lab data sets. For the following analyses, I determined the percent of individuals who were normal at baseline and then exceeded outlier criteria during the study, by treatment group. I used the sponsor's outlier criteria from Exhibit 7.3.1.-1 for most of the lab tests. For bilirubin, I used 35µmol/L (sponsor used 43µmol/L) and for GGT, I used ≥100U/L as the outlier criteria instead of the ULN. Since the

percentage of subjects with thyroxine results below LLN was similar between treatment groups, and the sponsor had previously demonstrated treatment related differences for this test, I selected a more extreme outlier criterion (<40nmol/L) to compare groups. For absolute neutrophil count, I determined the number of subjects with an ANC≥2,000 at baseline and dropped below $1.5x10^9$/L, and/or $1.0x10^9$/L during the study.

Outliers for chemistry tests, OT/PE1

Test (outlier criteria)	Oxcarbazepine % outliers (n)	Placebo % outliers (n)
SGOT (≥100U/L)	0.8% (4/491)	0 (0/101)
SGPT (≥110U/L)	0.6% (3/487)	0 (0/101)
Total bilirubin (≥35µmol/L†)	0 (0/503)	0 (0/104)
GGT (≥100U/L)	1.1% (2/174)	0 (0/41)
LDH (≥500 U/L)	3.9% (16/411)	10.7% (10/92)
Creatinine (≥221µmol/L*)	0.2% (1/498)	0 (0/104)
BUN (≥14.3mmol/L‡)	0 (0/489)	0 (0/101)
Potassium (≤3.0mmol/L) (≥6.0mmol/L)	0.2% (1/466) 1.1% (5/466)	0 (0/99) 1.0% (1/99)
Sodium (≤125mmol/L) (≥154mmol/L)	2.9% (13/450) 0.7% (3/450)	0 (0/90) 1.1% (1/90)
Bicarbonate (<LLN) (>ULN)	18.3% (66/361) 19.9% (72/361)	24.3% (18/74) 43.2% (32/74)
Chloride (≤85mEq/L) (≥115mEq/L)	0.7% (3/446) 0 (0/446)	0 (0/88) 0 (0/88)
Thyroxine (<LLN) (<40nmol/L)	28.8% (117/406) 2.5% (10/406)	29.3% (24/82) 0 (0/82)

†≥2.0mg/dL *≥2.9mg/dL ‡≥40mg/dL

For creatinine, 3 subjects were identified with outliers but review of the lab values suggested data entry errors for 2 of the subjects so they were not included in the above table (NZ/11/9105 and NZ/14/9114 were normal, experienced 10 fold increases in creatinine, and then returned to normal on consecutive visits with no change in dose). The results in this table suggest that oxcarbazepine exposed subjects in study OT/PE1 had higher risks for high SGOT, SGPT, GGT. I reviewed the available lab data for the subjects with transaminase outliers in further detail. One of the patients identified using the sponsor's data set (OT/PE1CDN22569) reportedly had an outlier for SGPT (130U/L). A review of the CRF revealed that the SGPT was 15 U/L and that LDH=130U/L at that visit and therefore this subject was not included in the above table. The highest recorded SGOT was 354 U/L and the highest SGPT was 200U/L (same patient OT/PE1NZ119117). In the table below I present selected transaminase and total bilirubin results for subject OT/PE1NZ119117.

Lab results for subject OT/PE1NZ119117

Test	Visit 1 (baseline)	Visit 6 (dose 2400mg)	Visit 9 (dose 2400mg)	Visit 11 (dose 2400mg)	Visit 12 (dose 450mg)
SGOT	23 U/L	68 U/L	354 U/L	19 U/L	100 U/L
SGPT	34 U/L	50 U/L	200 U/L	36 U/L	59 U/L
Total bilirubin	5µmol/L	13µmol/L	9µmol/L	5µmol/L	12µmol/L

None of the subjects with outliers for SGOT or SGPT had a recorded total bilirubin >1.0mg/dL (17.1µmol/L). One patient with an outlier for SGOT (118U/L at visit 4) discontinued for an AE (repetitive tonic-clonic seizures, drowsiness). No other patients with transaminase outliers discontinued prematurely from this study.

Oxcarbazepine exposed subjects in OT/PE1 had a higher risk of low sodium, chloride and thyroxine outliers. I examined the sodium outliers by gender to look for differences. The percentages of males who had a normal sodium at baseline and at least one on treatment value below 125mmol/L was 2.9% (6/208), the same percentage observed in females (2.9%,7/243).

The following table displays the results of an outlier analysis of hematology test results for study OT/PE1.

Outliers for hematology tests, OT/PE1

Test (outlier criteria)	Oxcarbazepine % outliers (n)	Placebo % outliers (n)
Hemoglobin (<10g/dl)	0.2% (1/413)	0 (0/83)
Hematocrit (<30 vol %)	0.5% (2/430)	0 (0/86)
Platelet count (<100x10^9/L) (>600x10^9/L)	0.2% (1/458) 0 (0/458)	2.1% (2/96) 0 (0/96)
WBC count (<3x10^9/L)	1.1% (5/451)	2.1% (2/94)
ANC (<1.5x10^9/L) (<1.0x10^9/L)	1.6% (7/441) 0.5% (2/441)	7.7% (7/91) 1.1% (1/91)

In study OT/PE1, oxcarbazepine exposed subjects did not experience notable increases in risk for outliers for the displayed hematology tests.

4.11.2.3 Transaminase and Total Bilirubin Outliers, all Oxcarbazepine Exposed

To further investigate subjects with liver lab test abnormalities, I used the sponsor's electronic data set to search the AST, ALT and total bilirubin results for all subjects exposed to oxcarbazepine. From the subjects with normal results at baseline, I identified those with at least one AST or ALT ≥3 times the upper limit of normal or with a bilirubin>35μmol/L (2mg/dL). I identified 24 oxcarbazepine exposed subjects who had 1 or more transaminase results meeting the stated criteria. The highest recorded AST was 354U/L and the highest recorded ALT was 228 U/L. None of the 24 identified subjects with transaminase outliers had a total bilirubin that was greater than 1.0mg/dL, although 3 of these subjects did not have total bilirubin measured. In most cases the abnormalities resolved while on drug, or with dose reduction, but there were instances where the greatest abnormality was the last recorded value (OT/F04RA122, 004USAM8456A107, 004USAM8464U108, FTRI02F9932).

There were 4 oxcarbazepine exposed individuals who had normal total bilirubin results at baseline and at least 1 abnormality recorded during a study. The highest recorded bilirubin was 47.9 μmol/L (2.8mg/dL). For three of these patients (OT/F01BR2709, OT/F10D303218, OT/F10D304205), the abnormality was an isolated event, with no associated increase in transaminases, that resolved by the next measurement without changes in the dose. For the last subject (OT/PE1ERA113105) the abnormality was recorded at the last visit. This patient had a serious AE (increased seizures) but no liver related adverse events were noted.

4.11.3 Sodium Decline by time

I examined the mean drop in sodium over time to look for evidence of a progressive decline with time. Using the chemistry data set provided by the sponsor, I identified the oxcarbazepine treated subjects from study OT/PE1. For selected visits, I calculated the mean change from baseline and identified outliers for sodium. The results of that analysis are provided in the table below.

Sodium mean change from baseline and outlier by visit/study week

Visit Number (study week)	Mean Δ from baseline (n tested)	Outliers (Na^+≤125mmol/L)
Visit 6 (week 3)	-2.1 (n=329)	3.3% (11/329)
Visit 7 (week 6)	-1.3 (n=298)	1.3% (4/298)
Visit 9 (week 14)	-1.5 (n=260)	1.2% (3/260)
Visit 11 (week 22)	-1.5 (n=225)	0.9% (2/225)

The results from the above analysis demonstrate a decrease in sodium and suggest that the greatest change occurs in the first weeks following initiation of therapy.

4.11.4 Outliers on Consecutive visits

The sponsor used a different approach in another set of outlier analyses, they included only patients with abnormal values on 2 consecutive visits. Although this may help increase the specificity for selecting patients with abnormal test results, subjects dropping out after a single abnormal result or subjects with abnormalities that fluctuated above and below the abnormal threshold would be missed in these analyses. The results of these analyses were included in sponsor's exhibit 7.3.2.-1 (adjunctive therapy and monotherapy substitution) and 7.3.3.-1 (initiation of monotherapy). For the adjunctive therapy and monotherapy substitution trials, I identified those tests where the abnormality was present in consecutive visits in at least 1% of oxcarbazepine subjects and occurred at least twice as frequently compared to placebo. Those results included low uric acid (1.8% OXC, 0.3% PLB) high cholesterol (8.1% OXC, 0 PLB), and low T_4 (8.6% OXC, 2.9% PLB). For the initiation of monotherapy trials there were only 2 oxcarbazepine subjects who met outlier criteria on consecutive visits (both for low T_4).

4.11.5 Urinalysis data

Since the sponsor did not provide a review of the urinalysis results in the lab review section of the ISS or safety update, I requested an analysis of these data. I suggested that the sponsor provide a summary of the results from trial OT/PE1. The sponsor provided several tables including treatment emergent abnormal urinalysis values, treatment emergent abnormal urinalysis values occurring at consecutive visits, a listing of the subjects with abnormal values at consecutive visits, and a summary of changes from baseline to final lab result.

In sponsor's table 1, Treatment emergent markedly abnormal urine values (7/7/99 submission p.9) there did not appear to be an increased risk for an abnormality detected from urinalysis testing among oxcarbazepine subjects. Again, when viewing treatment emergent urinalysis abnormalities at consecutive visits (table 2, p.10, 7/7/99 submission) there was no evidence of an increased risk among oxcarbazepine subjects. From the sponsor's listing (table 3, p.11, 7/7/99 submission) one oxcarbazepine subject (subject A/1/826/ 3510, urine blood) and one placebo subject (GB/15/890/8009, urine blood) had abnormalities on consecutive visits considered clinically relevant. The sponsor commented that follow up for the oxcarbazepine subject is pending. In sponsor's table 4 (p. 12, 7/7/99 submission), the risk of developing hematuria or proteinuria among the subjects "normal" at baseline was a similar for oxcarbazepine and placebo exposed groups. The results from study OT/PE1 did not provide evidence of an increased risk of urinalysis abnormalities among oxcarbazepine exposed subjects.

4.11.6 Discontinuations for Laboratory Abnormalities

The sponsor provided a listing of oxcarbazepine exposed patients who discontinued for laboratory result abnormalities (listings 6.4.-5, 6.4.-6, Safety Update). The sponsor listed 14 oxcarbazepine subjects who withdrew for lab abnormalities. I reviewed the narratives for these subjects. Six oxcarbazepine subjects withdrew for hyponatremia, 1 for hyponatremia and leukopenia, 1 for elevated alkaline phosphatase, 1 for elevated glucose, 2 for transaminase elevations and 2 for leukopenia. Information from one of the narratives (NGB9027 GB/1/103/A3) suggested that this patient's event (anemia) occurred on placebo. The sponsor included a narrative for an oxcarbazepine patient who discontinued for hyponatremia (028/USAM0592T/598) but this subject was not included in the listing of discontinuations for lab abnormalities. For the two patients discontinuing for transaminase elevations (026EUSAM8713E/103/526, OT/E25/F/74/35) I reviewed all relevant liver testing data included in the electronic data set. For subject 103/526 the highest transaminases were SGOT 84 and SGPT 130 and the highest total bilirubin was

0.8mg/dl. For the patient F/74/35 the highest transaminase results were SGOT 350U/L and SGPT 289U/L and the lab results did not include total bilirubin.

4.12 Vital Signs

The sponsor's approach to presenting vital sign changes was to provide the percentage of patients with clinically significant changes in pulse, SBP, DBP, and body weight for all trials, for the adjunctive therapy/monotherapy substitution trials, and for the initiation of monotherapy trials. The sponsor used the following criteria to identify clinically significant changes in vital signs:

Exhibit 2.4.3.-1. Criteria for identifying vital signs as clinically notable[1]

Variable	Age Group	Criterion value	Change relative to baseline
Pulse rate	<12 years	>130 bpm	Increase of ≥15
	<12 years	<70 bpm	Decrease of ≥15
	≥12 years	>120 bpm	Increase of ≥15
	≥12 years	<50 bpm	Decrease of ≥15
Systolic BP	<12 years	>125 mmHg	Increase of ≥20
	<12 years	<70 mmHg	Decrease of ≥20
	≥12 years	>180 mmHg	Increase of ≥20
	≥12 years	<90 mmHg	Decrease of ≥20
Diastolic BP	<12 years	>85 mmHg	Increase of ≥15
	<12 years	<40 mmHg	Decrease of ≥15
	≥12 years	>105 mmHg	Increase of ≥15
	≥12 years	<50 mmHg	Decrease of ≥15
Weight	<12 years	none	Increase ≥13% per 6 months of exposure to trial drug
	<12 years	none	Decrease ≥7% per 6 months of exposure to trial drug
	≥12 years	none	Change of ≥7% body weight

The following table provides the vital sign outliers from the adjunctive therapy and monotherapy substitution trials by treatment and age groups (ISS p.209). There did not appear to be any notable differences in the percentages of drug and placebo exposed subjects with vital sign outliers.

Exhibit 8.2.2.-1 Clinically notable[1] change in vital signs and body weight (placebo-control adjunctive therapy and monotherapy substitution in patients with epilepsy)

		Oxcarbazepine				Placebo			
	Clinically notable	<12 years all doses		≥12 years all doses		<12 years all doses		≥12 years all doses	
Variable	change	n	%	n	%	n	%	n	%
Pulse	total	71	100.00	1015	100.00	65	100.00	286	100.00
	decrease	5	7.04	7	0.69	5	7.69	1	0.35
	increase	0	0	7	0.69	4	6.15	3	1.05
Systolic BP	total	71	100.00	1016	100.00	65	100.00	286	100.00
	decrease	0	0	42	4.13	4	6.15	21	7.34
	increase	2	2.82	7	0.69	7	10.77	1	0.35
Diastolic BP	total	71	100.00	1016	100.00	64	100.00	286	100.00
	decrease	2	2.82	20	1.97	2	3.13	15	5.24
	increase	2	2.82	18	1.77	2	3.13	5	1.75
Body Weight	total	71	100.00	1111	100.00	66	100.00	269	100.00
	decrease	6	8.45	77	6.93	6	9.09	22	8.18
	increase	5	7.04	113	10.17	4	6.06	36	13.38

Source: Tables 8.2.2.-3, 8.2.2.-7, 8.2.2.-11, and 8.2.2.-15

The results comparing the treatment groups from the initiation of monotherapy studies (not shown) were similar to above with the exception that the oxcarbazepine >12 year old group had higher percentages of both weight increase (24.9% v. 15.7%) and weight decrease (9.6% v. 3.9%) compared to the placebo group.

4.13 ECG analyses

Within the NDA the sponsor summarized ECG data collected during the development program. The sponsor stated that they performed baseline and termination ECGs in 13 of the studies (3-CP studies, 9-double blind trials, 1-open label trial) included in the NDA. In their analysis of these data, the sponsor sent the baseline and termination ECGs from studies 011, 025, and 026 to a central laboratory for reading (p.211 ISS). For the ECGs from the 3 included protocols, there did not appear to be any notable differences in the mean changes from baseline for QRS, PR, or QT when comparing the oxcarbazepine and placebo groups or among the different oxcarbazepine dose groups. In addition, the sponsor identified a single oxcarbazepine patient from these studies with an abnormal ECG (PR=240msec). The sponsor also reported that no patient in any trial had an ECG reading associated with an adverse event (p.211 ISS). The sponsor included narratives for patients who had ECGs that were labeled clinically significant at end study. Patient OT/PE1E/RA/22/3316 had a normal baseline ECG and developed palpitations during the study. A 24-hour monitor detected frequent polymorp and bigeminate ventricular extrasystoles. He was discontinued from the open label trial but continued on marketed oxcarbazepine. Other documented changes included development of poor R wave progression (USA/M0665Y/539), tachycardia/LBBB/repolarization changes (USA/M0945Y/617), and right axis deviation (OT/PE1E/D/8/1045).

4.14 Special Studies/Reports

4.14.1 Expert report on hyponatremia

The sponsor included a report on oxcarbazepine associated hyponatremia written by Dr. Alan Wasserstein. He defined clinically significant hyponatremia as < 125mEq/L and explained that serious symptoms usually require serum sodium below 115mEq/L. Dr. Wasserstein provided background information about incidence, prevalence, morbidity, and mortality associated with hyponatremia but did not address whether epileptic patients were at increased risk for hyponatremia or had increased sensitivity to changes in serum sodium. He described the symptomatic manifestations of acute hyponatremia, which include headaches, nausea, vomiting, tremors, delirium, seizures, decerebrate posturing and cerebral edema, which can progress to herniation. He explained that symptom severity is related to the magnitude of the drop as well as the rate of decrease and that acute hyponatremia occurs in less than 48 hours or with a fall of 12mEq/L per day. Chronic hyponatremia can cause anorexia, nausea, vomiting, cramps, personality change, gait disturbance, stupor, and rarely seizures. Dr. Wasserstein stated that even those with severe neurological signs including seizures from chronic hyponatremia do not manifest cerebral edema by CT scan and uncal herniation does not occur. The major risk of chronic hyponatremia appears to be overly aggressive correction, which can result in osmotic demyelination syndrome.

Dr. Wasserstein reviewed results of published studies that examined the effect of oxcarbazepine on serum sodium. He stated that in one study, the incidence of serum sodium<135mmol/L was 23% in oxcarbazepine exposed patients. He reviewed the data related to hyponatremia from the oxcarbazepine NDA database. The incidence of sodium<135mmol/L was roughly 22% (423/1,966) and the incidence of sodium<125mmol/L was 2.7% (54/1,966). Dr. Wasserstein commented that there is some evidence in the safety database for a dose response relationship for decrease in sodium although he described the relationship as variable and not monotonic. He identified a single patient from the NDA database with a sodium below 118mmol/L (110mmol/L)

and pointed out that the individual was asymptomatic. The incidence of sodium <125mmol/L was 0.5-0.6% in children younger than 18 years old and seemed more common in those >65 based on limited data. Dr. Wasserstein concluded that the bulk of the decline in sodium occurred at the earliest time of measurement (7.1.1.-3) and that continued treatment was associated with modest further reduction. In addition he suggests that the decline in sodium occurs early but is not "precipitous". This conclusion was based on results from a study in which 51 patients were rapidly titrated to high doses (day 1: 1,500mg, day 2-10: 2,400mg) and the finding that the 11 who developed hyponatremia below 135mmol/L did so within a mean of 7.6 days (One patient had a sodium at/below 125mmol/L). He concluded that there was no relationship between hyponatremia and adverse events including headache, nausea and vomiting, abnormal thinking, convulsions, or altered sensorium based on an analysis performed by the sponsor that provided the percentage of patients exposed to oxcarbazepine reporting these events stratified by their serum sodium. Dr. Wasserstein reported that in all cases, hyponatremia resolved completely when oxcarbazepine was reduced or discontinued or patients were treated symptomatically.

Dr. Wasserstein reported the results of a study conducted to examine the hyponatremia effects of oxcarbazepine. The study involved giving a water load to a group of epilepsy patients (n=11) and a group of healthy volunteers (n=10) prior to and during exposure to oxcarbazepine (maximal tolerated dose). Prior to exposure to oxcarbazepine, excretion of the water load, and minimal urine osmolality was normal in both epileptic and normal volunteers. The epilepsy patients tolerated higher oxcarbazepine doses compared to the volunteers (epilepsy 600mg n=1, >1,200-1,800mg n=1, >1,800mg n=8, 1 dropout; volunteers 600-1,200mg n=9, >1,800mg n=1). Following exposure, one epilepsy patient developed hyponatremia prior to the water load (Na=121mmol/L) and 2 normal volunteers developed hyponatremia during the water load (Na=124mmol/L, Na=119mmol/L). During exposure and water load, a statistically significant decline in serum sodium and plasma osmolality was observed. The percentage of water load excreted within 4 hours was 31.8% in epileptic patients and 54.1% in healthy volunteers (normal is 80%). Seventeen of 19 subjects failed to excrete 80% or more of the water load. He interpreted this finding as evidence of a physiologic rather than idiosyncratic drug effect. The minimal urine osmolality was 485 mOsm/L in epileptic patients and 253 mOsm/L in healthy volunteers (normal following water load is <100 mOsm/L). Dr. Wasserstein reports that these results indicate "severe impairment of water excretion, more severe in epileptic patients than in healthy volunteers". In addition, he concludes that epileptic patients could never produce urine more dilute than plasma, that is, urine osmolality never fell below 300mOsm/L. Regarding etiology, Dr. Wasserstein found that plasma arginine vasopressin levels during water load were similar to those prior to oxcarbazepine treatment and that urine osmolality during water load was inappropriately high, which is compatible with either increased renal tubular sensitivity to ADH or an ADH independent effect on renal tubular water reabsorption.

Based on the results of the water load study, Dr. Wasserstein felt that oxcarbazepine's effect on free water reabsorption should have resulted in more severe hyponatremia than was observed in the NDA safety database. He proposed several possible reasons for not observing that finding including compensatory responses analogous to reset osmostat, oxcarbazepine-induced suppression of ADH limiting water retention at low sodium levels, and oxcarbazepine related hypodipsia.

Dr. Wasserstein provided information comparing the effect of oxcarbazepine with carbamazepine. In a 1-week study using a dose of 600mg of carbamazepine, subjects had a lower urine osmolality following water load (100-200mOsm/L) and serum sodium did not fall. It is unclear if these differences between oxcarbazepine and carbamazepine are due to drug or are explained by the different doses or duration of use employed in the studies. He indicated that the

most likely cause of carbamazepine induced hyponatremia is increased renal tubular sensitivity to ADH.

In his summary and conclusions section, Dr. Wasserstein states that from the NDA experience, hyponatremia due to oxcarbazepine has not usually been associated with clinical symptoms and that discontinuations have been rare. He notes that symptomatic hyponatremia has been reported in the literature and that the patients recovered with discontinuation. He concluded that children are resistant to oxcarbazepine induced hyponatremia and that the elderly may be at increased risk based on limited information. He felt that the evidence suggests that drug induced hyponatremia may occur more frequently with oxcarbazepine than with carbamazepine. He states that oxcarbazepine "can be reckoned safe on three grounds: first, the incidence of hyponatremia with the potential to be clinically symptomatic (serum sodium below 125mmol/L) is relatively low; second, serum sodium has very rarely fallen below 115mmol/L (1 case); and third, hyponatremia due to the drug will almost always be of the chronic type and therefore unlikely to cause severe consequences such as seizures or cerebral edema". He concedes that hyponatremia could be exacerbated by conditions including use of diuretics, other AEDs, other drugs that impair water excretion, smoking, volume contraction, or high fluid intake.

Dr. Wasserstein provided guidelines for safe use of oxcarbazepine. He recommended that patients taking oxcarbazepine should avoid high fluid intake and suggested that smoking should probably be avoided. He emphasized caution with pre-existing hyponatremia, psychogenic polydipsia, and concomitant use of medications such as carbamazepine, chlorpropamide, thiazide diuretics, phenothiazines, and tricyclic antidepressants. Dr. Wasserstein recommended measuring serum sodium prior to administration of oxcarbazepine. In addition, he recommended that serum sodium should be measured in patients demonstrating symptoms compatible with hyponatremia and in other patients as part of their routine laboratory studies. He suggested that monitoring of serum sodium levels should be more frequent in susceptible populations including: patients with conditions or medications known to impair water excretion or increase water intake; patients with acute pain, nausea, or extracellular volume contraction, and post-operative patients; patients with pre-existing hyponatremia. If serum sodium is below 125mmol/L, water intake may be restricted and/or dose of oxcarbazepine reduced. If oxcarbazepine cannot be reduced without worsening of seizures, the drug could be continued in unchanged dose with frequent serum sodium measurements. He suggested that concomitant acute illnesses or symptoms including headache, nausea, or confusion are indications for repeat serum sodium determination. Continued treatment with oxcarbazepine in this setting requires that the physician weigh the benefits of the drug in intractable seizure disorder against the risk of symptoms of chronic hyponatremia. He stated that rapid correction of hyponatremia with hypertonic saline is rarely if ever required and poses greater risk than that of hyponatremia itself.

4.15 Withdrawal Phenomena/Abuse Potential

On p.2 of NDA section 8I, the sponsor stated that in a study assessing psychological dependence in 4 monkeys, no clear drug seeking behavior was observed. There have been no clinical trials specifically designed to evaluate the abuse potential of oxcarbazepine. The sponsor commented that there have been no reports of withdrawal syndrome in subjects discontinuing oxcarbazepine after a duration of therapy of up to 4 years (ISS p.258).

4.16 Human Reproduction Data

The sponsor knows of 47 pregnancies in patients receiving oxcarbazepine (Safety Update p. 113). Twenty-five were from the primary database, 2 from the named patient program, and 20 from post-marketing reports. A table identifying the pregnancies and available information about outcomes is provided as an appendix to this review. For the 25 pregnancies from the primary

database, 8 were reported as induced abortions with no additional information about the presence or absence of fetal anomalies. Ten pregnancies resulted in normal babies, 1 ended in miscarriage during the first trimester, 4 had unknown outcomes, and 2 pregnancies were not completed at the time of reporting. For the two pregnancies from the Named Patient Program, one resulted in a miscarriage at 12 weeks (no evidence of malformations) and the other resulted in a normal baby. For the 20 pregnancies identified from post-marketing reports, 9 resulted in normal babies, 2 in spontaneous abortions (1-anembryonic pregnancy), 1 pre-mature delivery at 22 weeks resulting in death (no evidence of malformations), 1 baby with an unspecified heart malformation, 3 babies with cleft-palates, 1 baby with an epicanthal malformation, 2 low birth weight babies, and 1 birth with an unknown outcome.

4.17 Overdose Experience

On p. 2 of section 8I of the NDA, the sponsor stated that the LD_{50} in the mouse and rat were >6,000mg/kg which corresponds to a dose 175 times the maximum recommended human dose (2,400mg) for a 70kg human. The sponsor reports knowledge of 6 cases of overdose with oxcarbazepine from clinical trials, all suicide attempts. All 6 reportedly recovered without sequelae. Overdose symptoms included somnolence, dizziness, nausea, vomiting, hyperkinesia, hyponatremia, severe gait instability, ataxia, and nystagmus. The highest recorded dose ingested was 24,000mg (10 times above the highest recommended dose) and in one case, the ingested dose was not determined. One of the overdose patients was treated for hyponatremia and there were no reports of cardiac rhythm abnormalities or respiratory depression among overdose cases.

4.18 Drug-Drug Interactions

In an overall summary, the sponsor noted that in vitro, MHD was a weak inhibitor of CYP2C19 and CYP2C9 and a weak inducer of UDP-glucuronyltransferase. The sponsor observed an effect of MHD on the plasma concentrations of phenobarbital (mean increase of 15%) and phenytoin (mean increase of 40%) in patients receiving oxcarbazepine doses >1,200mg in a safety study. The sponsor commented that the interaction between phenytoin and MHD was not observed in other polytherapy trials. Oxcarbazepine induces the subgroup of CYP450 enzymes of the 3A family, which is responsible for the metabolism of dihydropyridine calcium antagonists (felodipine) and oral contraceptives. Decreases in the levels of felodipine (28%) were observed with repeated administration of oxcarbazepine. Mean AUC values of EE and LNG (hormonal components of an oral contraceptive) were decreased by 48/52% and 46/52% respectively, which could lead to contraceptive failure. Carbamazepine, phenobarbital and phenytoin reduce MHD levels by 30-40% when administered with oxcarbazepine. The sponsor provided the following table to summarize drug-drug interactions for AEDs.

Exhibit 9.2.-1 Summary of AED interactions with OXC

AED Co-administered	Effect of OXC/MHD on AED Concentration	Ref.	Effect of AED on OXC/MHD Concentration	Ref.
Carbamazepine	0-22% decrease (30% increase of Carbamazepine-epoxide)	[6,12,16]	40% decrease	[12]
Clobazam	NS		No influence	[17]
Felbamate	NS		No influence	[18]
Phenobarbital	13-14% increase	[16,6]	30% decrease	[16,13,14]
Phenytoin	0-40% increase	[12,16,6]	29-35% decrease	[12,16]
Valproic acid	No influence	[12,16]	0-18% decrease	[12,16,13,14]

The sponsor explored AE risk by concomitant anti epileptic drug use in study OT/PE1. They found no consistent pattern indicating that the incidences of AEs differed as a function of concomitant AED treatment (ISS p.139). The sponsor did not provide analyses looking at differences in risk for AEs stratified by use of other concomitant medications for the clinical trials.

4.19 Drug-Disease and Drug Demographic Interactions

The sponsor reported on p. 230 of the ISS that the half-life of the metabolite, MHD, is prolonged in patients with moderate to severe renal impairment (Cr clearance <30ml/min) with a two-fold increase in the AUC. Mild to moderate hepatic impairment did not affect the pharmacokinetics of MHD. In epileptic children aged 2 to 5 years receiving up to 3 AEDs, the AUC values of MHD were 30% lower than in children aged 6-12 years following a single-dose administration of 5 and 15mg/kg of oxcarbazepine. After both single and multiple dose administrations in elderly volunteers (60-82 years), the MHD AUCs and maximal concentrations were [redacted] higher than in younger volunteers (18-32years). The sponsor did not provide analyses looking for differences in AE risk stratified by the presence of underlying diseases for the clinical trials.

4.20 Review of the Medical Literature

The sponsor provided a review of the medical literature in the ISS and Safety Update through 8/31/98. They identified 456 publications that mentioned oxcarbazepine. These publications included abstracts, case reports, case series, retrospective descriptive studies, and controlled trials. There did not appear to be evidence of unique or previously unrecognized adverse events in the publications that contained safety information. In a fax dated 4/1/99, the sponsor forwarded a report from the literature of 2 sudden deaths in patients treated with oxcarbazepine from Norway. In the first case, the patient was switched from carbamazepine to oxcarbazepine. His serum sodium on the day of the switch was 125mmol/L. He died suddenly on the fifth day of oxcarbazepine therapy and his serum sodium on the day of death was 117mmol/L. Post-mortem vitreous humor analysis confirmed hyponatremia and additional lab results were consistent with inappropriately concentrated urine. The second case was a sudden death in a patient who had been treated with a regimen of oxcarbazepine, lamotrigine, and vigabatrin for 2 years prior to his death. Vitreous humor sodium collected during autopsy revealed a sodium of 124mmol/L.

5.0 Review of Systems

5.1 Cardiovascular

The sponsor did not identify any cardiovascular related toxicity in their summary of animal studies and there did not appear to be any specific cardiovascular related safety concerns raised in the proposed labeling. There were many sudden/unwitnessed deaths in the development program and it was not possible to exclude cardiac etiology for many of these events. In reviewing serious adverse events, cardiovascular events were not commonly reported. Looking at the comparative data from controlled trials, there did not appear to be an excess of serious cardiovascular events among the oxcarbazepine-exposed subjects. Cardiovascular events did not commonly lead to discontinuation and there did not appear to be an excess of any cardiovascular events leading to dropout among oxcarbazepine-exposed subjects when viewing the controlled trial data. Again, when viewing treatment emergent events, cardiovascular events were not commonly observed. Two cardiovascular events were reported by more than 1% of exposed subjects (hypertension 1.5%, 33/2,224 and syncope 1.1%, 24/2,224). In the adjunctive therapy/monotherapy substitution trials there was an excess of hypertension AEs (0.8%, n=10) among oxcarbazepine exposed individuals compared to placebo exposed (n=0) and an excess of syncope AEs among oxcarbazepine exposed (0.6%, n=7) compared to placebo (0.3%, n=1). In the initiation of monotherapy trials a similar pattern was observed for hypertension (1.4%, n=6 for oxcarbazepine and n=0 for placebo) but not for syncope (2.5%, n=11 for oxcarbazepine, 3%, n=2 for placebo).

The sponsor's vital sign analyses did not suggest an increased risk of high blood pressure outliers associated with oxcarbazepine exposure. I conducted an additional analysis looking at risk for systolic and diastolic blood pressure (SBP, DBP) high outliers. Using the sponsor's data set for study OT/PE1, I examined the risk of developing an increased SBP and DBP measurement for patients with a normal baseline (SBP≤140mmHg, DBP ≤90mmHg at visit 3, the last visit prior to initiation of oxcarbazepine). The results are included in the following table.

Blood Pressure Outliers from Study OT/PE1

	Systolic BP	
Outlier Criteria	Oxcarbazepine (n=433)	Placebo (n=161)
≥160mmHg	4.2% (18)	2.5% (4)
≥170mmHg	1.4% (6)	1.2% (2)
≥180mmHg	0.2% (1)	0.6% (1)
	Diastolic BP	
	Oxcarbazepine (n=494)	Placebo (n=168)
≥100mmHg	7.7% (38)	8.9% (15)
≥110mmHg	2.0% (10)	2.4% (4)
≥120mmHg	0.4% (2)	0.6% (1)

The results from this analysis did not suggest marked differences in risk for blood pressure elevation by treatment for subjects with normal measurements at baseline.

The sponsor's analysis of ECG data did not identify any substantial differences between drug and placebo. The sponsor's approach to analyzing ECG data, comparing a single baseline measurement to the final measurement and calculating the mean change for pooled data is not expected to be sensitive for exploring changes in a parameter such as the QT interval which is known to have substantial intrasubject variability.

I reviewed the secondary databases to identify cardiovascular events of interest. In the pre-GCP database a death was attributed to cardiopulmonary arrest with few additional details. In the named patient program there was a death attributed to coronary artery disease with documentation of coronary artery plaque rupture on autopsy. In addition, the named patient program identified 10 patients with serious cardiovascular AEs (angina, CAD/sudden death, MI, CHF, cardiac arrest, aortic aneurysm, vascular disorder, thrombophlebitis, and ventricular tachycardia with bundle branch block). There were 3 deaths from spontaneous reports that were possibly due to cardiovascular events. One death was only described as sudden, another was unwitnessed and occurred in a patient who developed complete heart block earlier in the day, and the last death mentioned cardiac arrest in a patient with aortic stenosis. In the post marketing reports there was a case of tricuspid regurgitation and RV dilatation in a patient taking oxcarbazepine and felbatol. In addition, there was a report of myocardial insufficiency in a 10 year old with pericardial effusion, edema and ascites. No explanation was found for the event. Symptoms initially improved following discontinuation of oxcarbazepine, but apparently ascites recurred off drug before disappearing completely. There were also several reports related to heart rate/rhythm including heart block (2), sino-atrial block (2), 2nd degree AV block (1), AV block (1), and bradycardia (1). Most of the cases were confounded by the use of medications known to effect cardiac conduction.

5.2 Central Nervous System

The sponsor did not identify any major CNS safety concerns in the summary of animal studies. Several of the oxcarbazepine deaths described by the sponsor were attributed to seizures, but these tended to be sudden or unobserved deaths and it is not possible to definitively determine the cause of death in many cases based upon the information provided. The CNS body system was

the most frequently reported for serious adverse events. Almost 6% (129/2,224) of exposed subjects experienced a serious AE in the CNS category and convulsions were the most commonly reported CNS SAEs (4.1%, 92/2,224). Eighteen oxcarbazepine exposed subjects had serious events coded as balance, gait or coordination disorders. Using narrative summaries and CRFs, I created a table to summarize these events (provided as an appendix to this document). The median duration of exposure prior to a serious balance/gait event was 17 days (range 4-893 days) and 11/18 patients experienced this event within 1 month of initiation of therapy. In many cases, the balance/gait symptoms were associated with other symptoms including nausea and/or vomiting (n=7), vertigo (n=5), diplopia (n=5), nystagmus (n=5), and drowsiness (n=3). Twelve of these subjects discontinued for these events and the symptoms resolved. For the remaining subjects, the symptoms resolved with or without dose reduction and the subjects continued in the trial.

In the adjunctive therapy/monotherapy substitution controlled trials 4.3% (55/1,272) of oxcarbazepine subjects, 2.3% (8/353) of placebo subjects and 3.7% (5/134) of carbamazepine subjects experienced CNS SAEs. In the initiation of monotherapy controlled trials 2.5% (11/440) of oxcarbazepine subjects, 4.5% (3/66) of placebo subjects, 2.5% (3/121) of valproate subjects and 1.3% (3/240) of phenytoin subjects experienced CNS SAEs. The risk for convulsion SAEs was similar across treatment groups in the controlled trials. There did appear to be a numerical difference in risk for events coded as Balance/gait disorders in the adjunctive therapy/monotherapy substitution trials (1.1%, 14/1,272 oxcarbazepine subjects; 0.7%, 1/134 carbamazepine subjects and 0/353 placebo subjects). CNS events commonly (13%, 295/2,224) led to discontinuation of oxcarbazepine subjects. Dizziness (4.8%, n=106), ataxia (4%, n=89), somnolence (3.2%, n=71), headache (2.3%, n=52) and nystagmus (2.1%, n=46) were the most common CNS events leading to discontinuation. In the adjunctive therapy/monotherapy substitution trials the risk for discontinuation for oxcarbazepine compared to placebo was 6.8% v. 1.4% for dizziness, 6.3% v. 1.1% for ataxia, 2.1% v. 0.3% for gait abnormality, 2.9% v. 0.3% for headache, 3.4% v. 0.8% for nystagmus, 1.9% v. 0.6% for tremor and 2.8% v. 0 for vertigo. These differences were not as pronounced in the monotherapy substitution trials. Again, when reviewing treatment emergent events, CNS AEs were commonly reported (71%, 1,583/2,224). The most commonly reported events were headache (33%, n=723), dizziness (29%, n=636), somnolence (26%, n=588), ataxia (12%, n=255), nystagmus (7%, n=156), insomnia (6%, n=128), gait abnormal (5%, n=121), depression (5%, n=113), and nervousness (5%, n=109). The following CNS events occurred more frequently in oxcarbazepine exposed subjects than placebo subjects in clinical trials and exhibited evidence of a dose response: dizziness, ataxia, vertigo, headache, somnolence, and tremor.

I reviewed the secondary databases to identify nervous system events of interest. There were no nervous system related deaths or SAEs identified from the pre-GCP database. In the named patient program, 2 deaths occurred following status epilepticus and a third death was attributed to brain stem thrombosis. In addition there were two serious AEs for seizure. Among the spontaneous post-marketing reports there was a death attributed to status epilepticus and another attributed to seizure. The nervous system spontaneous reports included events such as dizziness, ataxia, vertigo, dysarthria, nystagmus, confusion, stupor, encephalopathy, and status epilepticus. In addition there was a report of 3 patients on neuroleptics that developed extrapyramidal symptoms after being switched from carbamazepine to oxcarbazepine.

5.3 Dermatologic

The sponsor did not identify any potential drug associated dermatologic events from the summary of animal data. In the ***Precaution*** section of the proposed labeling, the sponsor states that patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that

approximately 25-30% of these patients might experience hypersensitivity reactions with oxcarbazepine and mentions severe skin reactions as an example. I did not identify any oxcarbazepine deaths with associated severe skin events. There were 13 reports of serious skin related events included under Skin and Appendages and Resistance Mechanism disorders from the clinical trial database through the safety update. Although some of these subjects were hospitalized, based on the narratives, none appeared gravely ill and most were treated briefly with oral medications (antihistamines or corticosteroids) and experienced prompt improvement. One report mentioned oral involvement (petechial lesions of the soft palate). None of the cases were diagnosed as erythema multiforme, Stevens Johnson syndrome, or toxic epidermal necrolysis. These serious skin events have been reviewed and summarized above. Skin related adverse events led to discontinuation of 3% (66/2,224) of those exposed to oxcarbazepine. In the adjunctive therapy/monotherapy substitution trials 1.7% (n=23) of oxcarbazepine patients dropped out for rash, rash erythematous or rash maculopapular compared to 0 placebo patients, 2.2% (n=3) carbamazepine patients and 1.9% (n=1) phenobarbital patients. In the monotherapy substitution trials, 2.3% (n=10) of oxcarbazepine subjects dropped out for rash, rash erythematous or rash maculopapular compared to 0 placebo patients, 5% of phenytoin patients (n=12) and 0 valproic acid patients. Overall, 21% (473/2,224) of oxcarbazepine subjects reported skin related AEs. After grouping the three rash events as above, the risk for rash in oxcarbazepine subjects from the adjunctive therapy/monotherapy substitution trials was 6.1% (n=77) compared to 3.4% (n=12) for placebo, 7.5% (n=10) for carbamazepine and 1.9% (n=1) for phenobarbital. In the monotherapy substitution trials the risk for rash in oxcarbazepine subjects was 9.3% (n=41) compared to 7.6% (n=5) for placebo, 12.9% (n=31) for phenytoin, and 4.1% (n=5) for valproate subjects.

The secondary databases were also reviewed to identify serious skin related adverse events. There were no serious skin related events in the Pre-GCP trials. In the Named Patient Program database, there were 7 skin related serious adverse events and we requested narratives for these patients for review. Most of the narratives mentioned rashes that were not well described. One event was diagnosed as Stevens Johnson syndrome and the patient had been exposed to several new medications immediately prior to the event including Augmentin, oxcarbazepine, clonazepam, and diphenytoin. Oxcarbazepine was discontinued and the patient recovered. I also reviewed the post-marketing report listings that were provided in the ISS and Safety Update. Skin related adverse events were the most frequently reported events in the post marketing listings (102/337). Through 8/31/98 there were 2 reports of exfoliative dermatitis, 3 reports of erythema multiforme, 2 reports of Stevens Johnson syndrome, and 1 report of toxic epidermal necrolysis (post-marketing estimate of exposure is 156,600 person years). As is usually the case with spontaneous reports, there was limited descriptive data available for these events. The sponsor commented that the toxic epidermal necrolysis case was not biopsy proven and that the event resolved upon discontinuation of oxcarbazepine and with continuation of comedications (sucralfate, amikacin, and fosfomycin).

5.4 Gastrointestinal

In the summary of the animal data, the sponsor noted morphologic hepatic alterations, which may have been associated with hepatic enzyme induction. I did not identify any GI related deaths in the primary clinical trial database. In reviewing the SAEs from the primary clinical trial database 1% (n=23) of patients developed serious GI AEs and 5 patients experienced a serious liver and/or biliary system disorder. Vomiting (n=6), and abdominal pain (n=5) were the 2 serious GI AEs occurring in more than 3 patients. The 5 serious liver and biliary AEs were reviewed (see above) and included 3 patients with evidence of hepatocellular injury/transaminase elevations and two patients with cholelithiasis. Gastrointestinal events commonly led to discontinuation from oxcarbazepine trials (7%, 154/2,224). Within this group, 4% (n=89) discontinued for vomiting and 3.7% (n=82) discontinued for nausea, the most common GI events leading to discontinuation.

In the adjunctive therapy/monotherapy substitution trials the percentages of oxcarbazepine subjects discontinuing for vomiting and nausea were 6% (n=78) and 5% (n=69) compared to <1% (n=1) and 1% (n=3) for placebo, 2% (n=2) and 1% (n=1) for carbamazepine and 2% (n=1) and 0 for phenobarbital. In the initiation of monotherapy trials the percentages of oxcarbazepine subjects discontinuing for vomiting and nausea were <1%(n=2) and 1% (n=5), compared to <1% (n=1) and 2% (n=1) for placebo, 0 and 2% (n=2) for valproic acid and 0 and 0 for phenytoin. There was a discontinuation for hepatitis and a discontinuation for an event labeled hepatic necrosis (SAEs described above). In addition there was a discontinuation for hepatic function abnormal (increased ALP) and 2 withdrawals for increased transaminases (described in the lab discontinuation section). Subjects commonly experienced treatment emergent GI AEs (47%, 1,036/2,224). The most commonly reported GI AEs were nausea 20% (n=442), vomiting 18% (n=397), abdominal pain 10% (n=224), diarrhea 8% (n=173), and dyspepsia 6% (n=131). In the adjunctive therapy/monotherapy substitution trials the risks for nausea, vomiting, and dyspepsia were higher in the oxcarbazepine group compared to placebo and exhibited dose response relationships. In the initiation of monotherapy trials, nausea, vomiting and dyspepsia were numerically more common among oxcarbazepine subjects compared to placebo but the relative risks were <1.5 and there did not appear to be dose response relationships. In addition to the hepatic events previously mentioned, 2 subjects (004EUSAM8459P101 and 026EUSAM8706P111) had events coded as jaundice. I reviewed the lab data for these two patients and the highest total bilirubin results were 0.7mg/dL and 0.5mg/dL respectively. Using the electronic data sets, I identified 7 subjects with AEs coded as liver enzymes elevated that were not serious and did not lead to discontinuation. In general these events involved increases of 2-3x ULN, none were associated with a total bilirubin>1.0mg/dL, and all resolved or improved either spontaneously or following decrease in dose.

I also reviewed the secondary databases to identify any events of potential concern. In the Named Patient Program (N=2,950) there was one GI related death (rectal adenocarcinoma). A subject from this database developed pancreatitis (SAE) on oxcarbazepine. In addition there were 2 patients reported with liver enzyme elevation adverse events and 1 patient with an adverse event of hepatocellular damage. In the pre-GCP trials, there were no reported GI related deaths or SAEs but 26 patients had elevated transaminases that were reported as AEs. A post-marketing report described a death in a patient who developed hepatic dysfunction on oxcarbazepine. Two months after being switched from carbamazepine to oxcarbazepine this 63 YO female had the following test results: ALP 461, AST 254, LDH 903 (no units). Oxcarbazepine was stopped and 4 days later she had the following results: ALP 358, AST 2,995, and LDH 4,125. She underwent a laparotomy (revealed hepatomegally and ascites) and subsequently developed wound rupture, sepsis and died. There was 1 spontaneous report of hepatitis with little supporting data. There was one spontaneous report of hepatic failure in a 6 year old who was also taking valproic acid. Another report described a patient who developed elevated transaminases (SGPT 727 U/L, SGOT 332 U/L, GGT 280U/L) 1 month after starting oxcarbazepine and 5 months after starting valproic acid. These tests normalized 1 week after discontinuing both drugs. There was a report of a patient hospitalized for abnormal hepatic function but with few details. In addition there were 2 spontaneous reports of pancreatitis (1 confounded by co-medications and the other reportedly improved while continuing oxcarbazepine).

5.5 Water balance/Hyponatremia

Because of the potential importance of these events, I am presenting the hyponatremia data separately from the metabolic or renal systems. In their toxicity summary, the sponsor did not identify electrolyte abnormalities as a concern. Association of hyponatremia and oxcarbazepine had been noted in the early development of this drug. In a special study in humans, the sponsor's expert consultant described hyponatremia that was the result of physiologic effect of the drug,

compatible with either increased renal tubular sensitivity to ADH or an ADH independent effect on renal tubular water reabsorption (see above). I did not identify any deaths that were specifically attributed to hyponatremia but several deaths were due to seizures and in many cases the sodium at the time of death was not known or not provided with the narrative. There were 14 subjects with serious AEs for hyponatremia (discussed above). The sponsor reported that 16 subjects withdrew from studies for hyponatremia. In the adjunctive therapy/monotherapy substitution trials 0.6% (7/1,272) of oxcarbazepine subjects withdrew for hyponatremia compared to 0.3% (1/353) of placebo subjects and no carbamazepine (134) or phenobarbital (52) subjects. In the initiation of monotherapy trials, 0.2% (1/440) oxcarbazepine subjects discontinued for hyponatremia compared to no placebo (0/66), phenytoin (0/240), or valproic acid (0/121) patients. Overall, 56 subjects (2.6%) developed hyponatremia that was reported as an adverse event. In the adjunctive therapy/monotherapy substitution trials the hyponatremia AE risk was 2.8% (36/1,272) compared to 0.3% (1/353) for placebo and 0 for carbamazepine (134) and phenobarbital (52). In the initiation of monotherapy trials the sponsor reported that 1 oxcarbazepine subject (0.2%, 1/440) had hyponatremia reported as an AE. Both the mean change from baseline and the outlier lab data support that oxcarbazepine exposure results in decreased serum sodium (see above). There did not appear to be a difference in risk for hyponatremia by gender. In the Safety Update, the sponsor summarized the risk for hyponatremia by age. The risk of a serum sodium<125mmol/L was 0 for the <6 year old group (n=69), 0.5% for the 6-11 year old group (1/211), 0.4% for the 12-17year old group (1/218), 3.8% for the 18-64 year old group (55/1443), and 7.3% for the ≥65 year old group (3/41). In study 011, a placebo controlled randomized adjunctive therapy trial in children (4-17 years old) the mean change from baseline for oxcarbazepine subjects was –0.2mEq/L compared to 0.1mEq/L for the placebo subjects (Table 9.6-4, p.448, study report 011). The sponsor reported that no oxcarbazepine subjects (n=135) and no placebo subjects (n=126) developed a serum sodium below 125mEq/L during this trial (Table 9.6-1, p.408, study report 011).

The sponsor examined the risk of treatment emergent adverse events stratified by a patient's lowest serum sodium during treatment. For the following events there appears to be the suggestion of a relationship between lowest serum sodium and risk for the event.

Incidence of treatment emergent adverse events by different serum sodium level groupings

Adverse event	Na≥135mmol/L (n=1493)	Na=125-134mmol/L (n=442)	Na<125mmol/L (n=60)	Total (n=1995)
Vomiting	16.4% (245)	21.7% (96)	23.3% (14)	17.7% (354)
Fatigue	13.7% (204)	22.2% (98)	23.3% (14)	15.8% (316)
Convulsions	1.7% (25)	2% (9)	6.7% (4)	1.9% (38)
Convulsions aggravated	1.9% (29)	3.1% (14)	5% (3)	2.3% (46)

For headache, dizziness, nausea, thinking abnormal and diplopia the risk was higher in the lower sodium groups but the relationship was not linear. The sponsor concluded, based on these data, that "patients with a serum sodium level below 125mmol/L showed a slightly higher rate of hyponatremia-associated symptoms compared to those patients with levels greater than 135mmol/L, but these differences are not considered to be clinically meaningful" (Safety Update, p.113).

I reviewed the secondary databases to identify any electrolyte disturbances (particularly hyponatremia) of potential interest. In the pre-GCP database, there were no deaths or serious adverse events that were attributed to hyponatremia. In the named patient program, there were several deaths attributed to seizures without information about serum sodium at the time of the event. In addition, one of the deaths occurred following status epilepticus and the narrative

mentioned cerebral edema on autopsy. The narrative for this patient stated that the patient had a recent biochemical screening that was satisfactory (no further details). There were 7 serious hyponatremia AEs in the named patient program, one associated with confusion and another with encephalopathy. In the post marketing/spontaneous report database no deaths were specifically attributed to hyponatremia but there was a death attributed to idiopathic brain edema in an "oligophrenic" female (no electrolyte results). There were two sudden deaths reported in the literature in patients with hyponatremia at the time of death although the exact relationship between hyponatremia and these deaths is not clear. In addition, there were a total of 22 serious hyponatremia reports, many without supporting details. The lowest serum sodium identified was 113mmol/L. Four reports mentioned associated convulsions or increased convulsions, and four reports mentioned associated mental status changes ranging from confusion to coma. The sponsor included a spontaneous report from the literature describing a 12 year old girl on oxcarbazepine with a sodium of 118 mmol/L. In this report, the authors also reported results of chart reviews of a cohort of children treated with oxcarbazepine. Nine of 48 oxcarbazepine exposed children with electrolyte measurements had a sodium level <135mmol/L, and except for the index case above, none had a recorded serum sodium below 125mmol/L.

Carbamazepine is also associated with hyponatremia. The sponsor's expert cited a 1 week study in which subjects receiving carbamazepine 600mg/day were administered a water load and were able to dilute their urine to a greater degree than the subjects in the oxcarbazepine water load study. It was unclear if this reflected decreased risk for hyponatremia or if the observed difference was due to differences in doses or designs of the studies. To compare the risks for hyponatremia for oxcarbazepine and carbamazepine, I reviewed the results from study OT/E25. Study OT/E25 was a double blind controlled trial in which subjects with newly diagnosed epilepsy or poorly controlled epilepsy were randomized to either oxcarbazepine tid or carbamazepine tid followed by a bid treatment phase. Subjects were titrated to fixed dose, the maximum target dose for oxcarbazepine was 2,100mg/day and for carbamazepine was 1,400mg/day. The sponsor reported that 128 subjects received at least one dose of oxcarbazepine and 134 received at least one dose of carbamazepine. The mean dose during the maintenance tid phase was 1,106mg (±340) for oxcarbazepine and was 720mg (±233) for carbamazepine. Prior to treatment, the serum sodium in the oxcarbazepine group was 143mEq/L, and in the carbamazepine group was 142.7mEq/L. In the table below, I present the mean sodium values for visits during the tid maintenance phase and the changes from baseline.

Mean sodium and change from baseline by visit and treatment group, study OT/E25

Visit number	Mean Na, oxcarbazepine	Change from baseline	Mean Na, carbamazepine	Change from baseline
Baseline	143	-	142.7	-
Visit 4	140.7	-2.3	142.1	-0.6
Visit 5	140	-3.0	142.1	-0.6
Visit 6	141	-2.0	141.9	-0.8
Visit 7	141.1	-1.9	142.1	-0.6
Visit 8	140.2	-2.8	142.1	-0.6

Data from table 9.6.-1, p. 350 vol 235

The data suggest slightly greater decreases in mean sodium for the oxcarbazepine group.

Subjects with serum sodium below 137mEq/L were considered to have an AE of hyponatremia. During this study, 10% (13/128) of oxcarbazepine subjects had a hyponatremia AE compared to 4% (5/134) of carbamazepine subjects. Exhibit 9.6.-1 on p. 82 of vol 235 provided the %/number of patients with abnormal lab values by treatment group for visits 4-8. Two and a half percent (3/120) of oxcarbazepine patients had a serum sodium result less than 125mEq/L during these studies compared to 0/128 carbamazepine subjects. In addition there was 1 discontinuation for an

AE of hyponatremia and 1 discontinuation for an abnormal lab result of low sodium in the oxcarbazepine group compared to none in the carbamazepine group.

Taken together, these data suggest that oxcarbazepine subjects were at an increased risk for decreases in serum sodium in this study.

5.6 Genitourinary/Renal
In their toxicology summary the sponsor mentions dose dependent and morphological renal alterations (enlarged kidneys in rats). In carcinogenicity studies of oxcarbazepine's metabolite, the sponsor found a marginal increase in the incidence of benign interstitial tumors of the testis and an increased incidence of granular cell aggregates or tumors in the cervix and vagina. I did not identify any GU/Renal related deaths in the clinical trial database. There were few GU/Renal SAEs (n=6, combining male, female reproductive disorders and urinary system disorders). These events included renal pain, impotence, ovarian cyst, unintended pregnancy, and abortion. In the hepatic CP/PK trial, a patient developed decreased creatinine clearance following exposure to oxcarbazepine that resolved (see above). GU/Renal AEs rarely led to discontinuation from oxcarbazepine studies (n=7) and no event led to discontinuation of more than 2 subjects. One subject discontinued for renal calculus (see above). In reviewing all treatment emergent AEs, GU/renal events were reported by 11% (n=252) of those exposed. The most commonly reported GU/Renal AEs were UTI (n=50), dysmenorrhea (n=48), menstrual disorder (investigator terms included change in menses, irregular menses, PMS n=23), dysuria (n=15), micturition frequency (n=15), genital disorder female (investigator terms included vaginitis n=14), and impotence (n=14). Two patients had renal calculus reported as an AE. There was one oxcarbazepine patient with uremia reported as an AE but the event was not serious and did not lead to dropout. This subject's highest recorded BUN was 17mg/dL and highest creatinine was 0.5mg/dL (chemistry data set). There were no events labeled renal failure or renal insufficiency. The overall risk for GU/Renal AEs was similar for oxcarbazepine (8%), placebo (8.5%), carbamazepine (6%), and phenobarbital exposed (7.7%) subjects in the adjunctive therapy/monotherapy substitution trials. UTI was the only AE occurring in at least 1% of oxcarbazepine exposed subjects (1.7%, n=21) and with a relative risk at least 2x higher than placebo (0.6%, n=2, RR=2.8) in these studies. In the initiation of monotherapy studies, the risk of GU/Renal AEs was higher for oxcarbazepine (10.7%, n=47) compared to placebo (3%, n=2) but was similar to phenytoin (10.4%, n=25) and valproic acid (13.2%, n=16). Analyses of the lab data by treatment group did not reveal any differences in BUN or creatinine that would suggest oxcarbazepine related renal toxicity.

I reviewed the secondary databases to identify GU/Renal events of potential interest. In the Named Patient Program, there were no deaths attributable to a GU/Renal cause and benign uterine polyp was the only serious GU/Renal AE identified. There were no deaths or serious GU/Renal AEs from the pre-GCP trials. For the post-marketing database, there were no spontaneous reports of deaths from GU/Renal causes and the only serious GU/Renal spontaneous report was for proteinuria in a 15 year old female taking oxcarbazepine (no other details).

5.7 Hematologic
The sponsor did not identify any specific hematologic concerns in their summary of the animal toxicology data. In the clinical trial database, there were no deaths attributed to hematologic etiologies. The sponsor reported that 2 subjects experienced serious white cell disorders (granulocytopenia, see above), 2 experienced serious platelet/bleeding/clotting disorders (hematoma) and 1 experienced a serious hemic and lymphatic reticuloendothelial disorder (pancytopenia, see above). The sponsor reported that a total of 8 subjects withdrew for events included in the hemic and lymphatic systems. Three withdrawals were for leukopenia, 1 for granulocytopenia, 2 for anemia and 1 each for lymphadenopathy, and thrombocytopenia. In

addition, using the discontinuation due to lab abnormalities listing, another 3 subjects withdrew for hematologic lab result abnormalities (all 3 for decreased WBC counts). I summarized the discontinuations for low WBC counts below.

004E/USA/M8456A/105/504 This 29YO female received placebo during the double blind phase of the trial and then entered the open label phase and was treated with oxcarbazepine 2,400mg/day. She was also taking phenytoin, lamictal and neurontin at the time. Her baseline WBC count was 4.1. After approximately 1 year of oxcarbazepine treatment, she developed neutropenia. Her lowest recorded WBC count was at visit 9 (WBC=2.5). She discontinued from the trial.
USA/M8712Z/120 This 33YO female was treated with oxcarbazepine 2,400mg/day and carbamazepine. Approximately 29 days after initiating oxcarbazepine, she was diagnosed with leukopenia. A review of her labs revealed that her baseline WBC count was low (2.5). Her visit 5 WBC count was 2.4 and her visit 6 (termination) WBC count was 3.8. The sponsor reported that following termination from the study her WBC count improved.
NI0C03/I/9/90 This 28YO female, treated with oxcarbazepine 900mg/day, developed "mild" leukopenia 12d after randomization. There were no WBC count results reported during the trial for this subject and the sponsor did not provide lab results that might have been collected outside of the protocol, therefore, the extent of leukopenia is not known.
026E/USA/M0206C/124 This 36YO female was treated with oxcarbazepine 2100mg/day, neurontin, lamictal, and topamax. Her baseline WBC count was 3.4. Six months after initiation of oxcarbazepine she developed a rash, dry cough, fever, and leukopenia. Lamictal and oxcarbazepine were stopped and the sponsor reported improvement in her condition. Her lowest WBC count was 2.8 (visit 17) and her WBC count appeared to be increasing on drug prior to discontinuation.
004E/USA/M8459P/103(502) This 54YO female was treated with oxcarbazepine 1,500mg/day in addition to phenytoin, carbamazepine, valium, ditropan, and hydrochlorothiazide. Her baseline WBC count was 2.7. She experienced increased seizure frequency and was hospitalized and diagnosed with hyponatremia and leukopenia (WBC count 2.3 in narrative). Using the sponsor's data sets, her lowest WBC count was 1.8 (visit 7) and it appeared that oxcarbazepine was stopped at that time. By visit 8, her WBC count had increased to 3.5 (off oxcarbazepine).
OT/E25/F/41/510 This 69YO female was treated with oxcarbazepine 900mg/day. Her baseline WBC count was 3.0. Twenty-eight days after randomization, her WBC count was 2.0 and she was terminated from the trial. No follow up was provided.
OT/PE1/C/1/2503(256) Case reviewed in SAE section.

Looking at the controlled trials, based on few events, there did not appear to be a substantial difference in risk for discontinuation due to hematologic events when comparing oxcarbazepine exposed and placebo/active control exposed subjects. Almost 4% (81/2,224) of oxcarbazepine exposed subjects reported a hematologic adverse event. The treatment emergent events occurring in more than one subject were anemia (n=33), leukopenia (n=15), lymphadenopathy (n=15), hematoma (n=12), granulocytopenia (n=4), and thrombocytopenia (n=3). Looking at the controlled trials, based on a small number of events, there did not appear to be a substantial difference in risk for hematologic treatment emergent AEs when comparing oxcarbazepine exposed and placebo/active control exposed subjects. From a review of the sponsor's lab analyses as well as my analysis of lab results from study OT/PE1, there did not appear to be affirmative evidence of oxcarbazepine related hematologic drug toxicity.

I reviewed the secondary databases to identify hematologic events of potential interest. In the Named Patient Program, there were no deaths due to hematologic causes but there were two serious hematological AEs (granulocytopenia, pancytopenia). I requested narrative summaries from the sponsor for these two serious events. The first patient, a 49YO female with a history of bone marrow suppression that pre-dated oxcarbazepine therapy, experienced a decrease in WBC count to 1.7 that was noticed approximately 8 months after initiating oxcarbazepine. The sponsor reported that her WBC counts increased "slightly" after discontinuing oxcarbazepine. The second

patient, a 16YO female, developed pancytopenia that was noticed 370 days after initiating oxcarbazepine. Bone marrow biopsy found decreased erythropoietic, myelopoietic, and megakaryopoietic lines. Within a month of discontinuing oxcarbazepine, her cell counts normalized. There were no hematological related deaths reported from the pre-GCP trials but there was a serious hematologic AE. This patient, a 33YO female, was diagnosed with pancytopenia and pneumonia approximately 20 months after initiating oxcarbazepine treatment and cell counts reportedly normalized upon discontinuation. For the post-marketing database, there was a death attributed to non-Hodgkin's lymphoma and 4 serious hematologic events. I reviewed the listings for these 4 events. In 3 cases (granulocytopenia, thrombocytopenia, and pancytopenia) there were very few details provided. For the 4th case (granulocytopenia with thrombocytopenia) a 21YO female who was also taking valproate, lamictal and clonazepam developed this event 7 days after initiating oxcarbazepine therapy and no further details were provided.

5.8 Metabolic/Endocrine
*Hyponatremia was included in the metabolic grouping in the sponsor's analysis but I split out the hyponatremia events and presented them separately (see above). This part of the review discusses the remaining events included in this category.

In their summary of toxicity studies, the sponsor mentioned thyroid follicular hyperplasia/hypertrophy were seen with oxcarbazepine's metabolite in rats. In a review of deaths from the primary clinical trials database, there were no events attributed to a metabolic/endocrine etiology. Metabolic/Endocrine events were rarely reported as serious AEs (n=2, hypocalcemia and hypokalemia). The sponsor listed one metabolic AE leading to premature discontinuation (thirst). There were 17 treatment emergent endocrine AEs in the primary database and hypothyroidism n=7, goiter n=3, thyroid disorder n=2, and endocrine disorder NOS n=2 were the events occurring in more than 1 subject. The sponsor reported that there were 28 metabolic AEs (excluding hyponatremia). The metabolic AEs included dehydration (n=12), thirst (n=9), diabetes mellitus (n=4), and obesity (n=3). Examination of the risks for these events in the controlled trials did not reveal substantial differences when comparing oxcarbazepine to placebo/active control subjects. Lab data analysis suggested that exposure to oxcarbazepine was associated with decrease in T_4 and possibly a decrease in T_3 but exposure to oxcarbazepine did not appear to be associated with changes in TSH (based on less data).

The secondary databases contained no metabolic/endocrine deaths, and few serious metabolic/endocrine SAEs. There was a spontaneous report of a 3 year old who apparently developed hypothyroidism (elevated TSH) that was associated with sadness, increase in sleeping, and periods of hyperactivity.

5.9 Respiratory
In their summary and discussion of toxicity data, the sponsor did not identify any respiratory system effects of oxcarbazepine or its metabolite. Three of the oxcarbazepine deaths in the primary clinical database were due to respiratory related events. One subject experienced cardiac arrest while being treated for pneumonia, a second patient's death was attributed to hypoxia following aspiration during a seizure, and the third subject died from acute laryngeal spasm that was attribute to an underlying condition (hyalinosis cutis). The sponsor reported 3 serious respiratory AEs from clinical trials database (laryngismus, asthma, and pneumonia). Respiratory AEs led to the discontinuation of 11 oxcarbazepine subjects from clinical trials and dyspnea was the only event leading to discontinuation of more than 1 subject (n=3). Almost 25% of those exposed (n=548) developed a treatment emergent respiratory AE. From the controlled trial

database, there did not appear to be evidence of substantial difference in risk for respiratory AEs when comparing oxcarbazepine exposed to placebo or active control exposed subjects.

I reviewed respiratory AEs from the secondary databases to identify events of potential interest. The sponsor did not report any respiratory related deaths from the pre-GCP database and the SAE from this group was for pneumonia and pancytopenia. In the named patient program, there were 5 deaths attributed to pneumonia, one to status asthmaticus, and one to lung cancer. There were 6 serious cases of pneumonia, 3 lung cancers, and a pulmonary fibrosis reported in the named patient program. I requested a narrative for the pulmonary fibrosis patient. This 80 year old male developed symptomatic, radiographic, and pulmonary function findings consistent with pulmonary fibrosis 29 months after starting oxcarbazepine. The sponsor reported that the patient was stable and apparently continued on oxcarbazepine. There were no pulmonary related deaths and no serious respiratory events identified from the post-marketing reports.

5.10 Musculoskeletal

The sponsor did not identify any musculoskeletal related concerns in their summary of the toxicity studies. There were no deaths attributed to musculoskeletal etiologies in the primary clinical trial database. The serious musculoskeletal AEs included joint dislocation, nerve root lesion, periarticular disorder, costochondritis and lupus erythematosus syndrome with pericardial effusion. The lupus event is summarized below.

OT/PE1E CDN2 2561/249 This 42YO male with a history of seizures treated with carbamazepine, was admitted for pleurisy and pericardial effusion requiring drainage, 16 months after initiation of oxcarbazepine. He was diagnosed with lupus (no details regarding work up). He was tapered off oxcarbazepine and carbamazepine and lupus was treated with prednisone. The narrative indicated that the event was attributed to carbamazepine, but oxcarbazepine could not be ruled out as an etiology.

Musculoskeletal events led to the discontinuation of 10 subjects. Muscle weakness (n=3), cramps muscle (n=2), and hypertonia muscle (n=2) were the musculoskeletal events leading to discontinuation of more than one subject. Musculoskeletal treatment emergent AEs were reported by 16% (344/2,224) of those enrolled. Arthralgia (n=70), and fracture (n=44) were the most commonly reported musculoskeletal AEs. In the adjunctive therapy/monotherapy substitution trials there did not appear to be substantial evidence of difference in risk for the treatment emergent musculoskeletal AEs. In the monotherapy substitution trials, arthralgia was reported by 3.6% (16) of oxcarbazepine exposed subjects compared to 1.5% (1) placebo exposed, 1.7% (4) phenytoin exposed, and 0.8% (1) valproic acid exposed subjects.

I reviewed the secondary databases to identify musculoskeletal events of interest. There were no musculoskeletal related deaths or SAEs in the pre-GCP database. In the named patient program there were no musculoskeletal related deaths and 2 fractures that were reported as serious adverse events. In the post-marketing reports there were no musculoskeletal related deaths. There were reports of lupus erythematosus, lupus erythematosus discoid, LE rash, and lupus like eruption which are summarized below.

A 51 YO female with a history of alcohol abuse and dementia developed a rash over sun exposed areas, non-erosive poly-arthtritis, Raynaud-phenomenom, and leucopenia. She was ANA+ (anti-histone antibody+). The arthritis, skin rash, and Raynaud-phenomenon resolved following discontinuation of oxcarbazepine. ANA screen remained positive but the anti-histone antibody became negative. No information about comedication was provided.
A 65YO male taking Flufenazin (fluphenazine), Pacisyn (?), and Saroten (amitriptyline) developed this event 487 days after initiating oxcarbazepine and completely recovered. No other details were provided.

A 45YO female taking Orafil (?valproate) with a history of discoid lupus on carbamazepine developed a facial rash and hair loss while taking oxcarbazepine.
A 29 YO female on phenobarbital and valproate developed a lupus like syndrome (skin rash and fever) approximately 1 month after initiation of oxcarbazepine. The report stated that the ANA was negative and that C3 and C4 were decreased. Outcome was "resolving".

5.11 Special Senses
The sponsor did not identify any concerns related to the specialized sensory organs in their summary of toxicity data. There were two serious events listed as vision disorders in the primary clinical trials database. In the first case a patient had diplopia associated with ataxia and mental slowing. Oxcarbazepine was discontinued and the subject completely recovered within 4 days. In the second case, a subject developed blurred vision and dizziness and oxcarbazepine was discontinued. Special sense AEs led to the discontinuation of 6% (n=142) of oxcarbazepine exposed subjects with diplopia (n=92), vertigo (n=36), and abnormal vision (n=33) being the most common events in this group. In the adjunctive therapy/monotherapy substitution trials 6% (79/1,272) of oxcarbazepine exposed subjects discontinued for diplopia compared to 0.6% (n=2) of placebo exposed and no carbamazepine or phenobarbital exposed subjects. Similarly, 2.8% (n=38) of oxcarbazepine exposed subjects discontinued for vertigo compared to no subjects exposed to placebo, carbamazepine or phenobarbital. The sponsor also reported that 2.4% (n=30) subjects discontinued for vision abnormal (mostly blurred vision) compared to 0.3% (n=1) placebo subjects and no carbamazepine or phenobarbital subjects. These findings were not replicated in the initiation of monotherapy trials where only 3 oxcarbazepine exposed subjects discontinued for events in the special senses category (conjunctivitis n=2, and eye complaint n=1). Almost 31% (n=688) of oxcarbazepine subjects developed treatment emergent AEs in the special senses category. Within this group, the most commonly reported events were diplopia (16%, n=360), vision abnormal (10%, n=225), vertigo (5%, n=109), ear infection NOS (2%, n=38 otitis where location not specified-media v. externa), and tinnitus (1%, n=22). There were 3 events coded as visual field defect and a single event coded as deafness. Within the adjunctive therapy/monotherapy substitution trials, the risk for diplopia in oxcarbazepine subjects was 17% (n=219) compared to 2.5% (n=9) in placebo subjects, 2.2% (n=3) in carbamazepine subjects, and 0 in phenobarbital subjects. The risk of vision abnormal was 10% (n=122) in oxcarbazepine subjects compared to 2.5% (n=9) in placebo subjects 4.5% (n=6) carbamazepine subjects and 0 phenobarbital subjects. The risk for vertigo in oxcarbazepine subjects was 7% (n=84), compared to 11.5% (n=6) in phenobarbital patients, 1.4%(n=5) in placebo patients and 0.7% (n=1) in carbamazepine subjects. There also appeared to be evidence of a dose response relationship for these three events (ISS table 5.2.2.-2). In the initiation of monotherapy controlled trials, vision abnormal was reported for 3.2% (n=14) oxcarbazepine subjects, no placebo subjects, 2.5% (n=6) phenytoin subjects and 5% (n=6) valproic acid subjects. There were only 2 reports of diplopia and 2 reports of vertigo in oxcarbazepine exposed subjects from these trials.

I reviewed the secondary databases to identify any special senses events of potential interest. The pre-GCP, Named Patient program, and post-marketing databases did not include any SAEs in the special senses category.

5.12 Body as a Whole
The sponsor included a wide variety of events within this category including allergic reactions (anaphylactoid), asthenia, edema, fatigue, fever, injury, trauma, pain, weight change and infections. During the review of coding, I became concerned about the effect of splitting investigator edema related terms into several preferred terms. In the following analyses, I grouped the preferred terms Edema, Edema Generalized, Edema Legs, Edema Dependent, and Edema Peripheral into a single edema category and examined risk differences between treatment groups.