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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-710

Medical Review(s)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21,710
Related NDAs	20,712 Carbatrol); ' (Carbamazepine)
Letter Date	February 13, 2004
Stamp Date	February 17, 2004
PDUFA Goal Date	December 13, 2004
Reviewer Name	Robert Levin, M.D.
Review Completion Date	November 22, 2004
Established Name	Carbatrol (extended release carbamazepine)
Proposed Trade Name	Equetra
Therapeutic Class	Anticonvulsant
Applicant	Shire
Priority Designation	S
Formulation	100 mg, 200 mg, 300 mg capsules
Dosing Regimen	400-1600 mg/day divided BID
Indication	Acute Mania
Intended Population	Bipolar Disorder, Manic Episode

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1. EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend that the Division take an approvable action for Equetra as monotherapy in the acute treatment of mania in adults with Bipolar Disorder. Two adequate and well-controlled trials demonstrated that Equetra was efficacious in the acute treatment of mania. Equetra treatment of manic subjects was reasonably safe and well tolerated. In my opinion, the estimated treatment effect of Equetra was clinically significant. Furthermore, it seems reasonable to expect that one could generalize from the results of these trials to the general population of Bipolar Disorder patients experiencing an acute manic episode, since the study population represented well the general population of patients with Bipolar Disorder with acute mania.

1.2 Recommendation on Postmarketing Actions- Phase 4 Commitments

In a meeting with the sponsor on November 1, 2001, the Division requested that the sponsor conduct well-controlled, long-term efficacy trials in subjects with Bipolar Disorder, Manic or Mixed episode. The Division stated that a randomized, double blind, placebo-controlled relapse prevention design would be necessary. An open-label continuation study will not suffice. The long-term studies could be undertaken as a phase 4 commitment.

1.3 .1 Overview of Clinical Program

Carbatrol (carbamazepine extended-release) is an approved and marketed anticonvulsant drug used for the treatment of epilepsy and trigeminal neuralgia. Equetra is the proposed trade name for carbamazepine extended-release for the indication of mania. There has been extensive clinical experience with both the extended-release and immediate-release formulations of carbamazepine. Moreover, clinicians have long treated Bipolar Disorder patients effectively with carbamazepine, targeting acute mania as well as the prevention of manic or depressive episodes. Equetra is administered orally.

The Equetra Mania clinical program consisted of 3 adequate, well-controlled trials and one open-label extension study. The two pivotal controlled trials were identically designed 21-day trials of Equetra monotherapy in acutely manic adult subjects with Bipolar Disorder (105.301 & 417.304). A third non-pivotal (failed), short-term, placebo-controlled study was nearly identically designed, except that the trial included only subjects who had been resistant to or intolerant to lithium (105.302). The fourth study was an open-label extension study of subjects who completed studies 105.301 or 417.304. Some of the subjects in the open-label trial had been treated with placebo in the acute trials. In this study (105.303) subjects were treated for up to an additional 52 weeks.

The review of efficacy will focus only on the two pivotal trials (105.301 & 417.304).
The safety review will include analysis of data from all 4 of the Equetra mania studies.

Overall, 299 male and female adult subjects (from the U.S. and India) were exposed to Equetra for a total of 31.7 person-years in the Equetra Bipolar Program. In the two pivotal trials (105.301 and 417.304), 223 subjects were exposed to Equetra for a total exposure of 9.82 person-years. In Study 105.302, 29 subjects were exposed to Equetra for a total exposure of 1.06 person-years. The long-term study included 92 subjects; 48 of these subjects had not been exposed to Equetra in the short-term trials. Equetra exposure in the long-term study was 20.8 person-years.

1.3.2 Efficacy

The efficacy results from both of the pivotal studies (105.301 and 417.304) indicate that Equetra monotherapy was efficacious in the treatment of acute mania for up to 21 days. The analysis of the pooled data also indicates that Equetra was efficacious.

The primary endpoint was the change in mean Young-Mania Rating Scale (YMRS) score between baseline and Day 21. The YMRS is the standard and most appropriate outcome measure for assessing treatment effects in acute mania. In Study 105.301, the baseline mean YMRS scores were 26.6 and 27.3 in the Equetra and placebo groups, respectively. The endpoint scores were 17.9 and 22.1 in the Equetra and placebo groups, respectively. Thus, the changes in mean YMRS at Day 21 were −8.7 and −5.2 in the Equetra and placebo groups, respectively. The difference was statistically significant (p=0.331), favor of treatment with Equetra. The results of Study 417.304 were similar. In this study, the baseline mean YMRS scores were 28.5 and 27.9 in the Equetra and placebo groups, respectively. The endpoint scores were 13.4 and 20.8 in the Equetra and placebo groups, respectively. Thus, the changes in mean YMRS at Day 21 were −15.1 and −7.1 in the Equetra and placebo groups, respectively. The difference was statistically significant ($p < 0.0001$), in favor of treatment with Equetra.

The estimated size of the Equetra treatment effect was a reduction in mean YMRS score of 3.5 and 8.0 in studies 105.301 and 417.304, respectively. In my opinion, the size of the Equetra treatment effect was clinically meaningful in both studies; although, the estimated size of the treatment effect was modest in study 105.301.

Subgroup analysis was performed for the variables: gender (male vs. female), age (age 18-39 vs. ≥ 40), race (Caucasian vs. non-Caucasian), and national origin (U.S. vs. India). No significant interaction effect of treatment group by any of the subgroup characteristics was found. The lack of significant interaction indicates that the treatment effect was similar irrespective of the patients' characteristics

The results of the key secondary endpoint analysis in the pivotal trials support the conclusion that the drug was efficacious in the treatment of mania in Bipolar Disorder. The secondary outcome measure was the Clinical Global Impression-Severity Scale (CGI-S). In both pivotal studies, there was a statistically significant difference between treatment groups in reduction of CGI-S, in favor of treatment with Bipotrol.

As these were fixed-dose studies, one cannot draw conclusions about a potential dose-response relationship. The sponsor monitored serum carbamazepine levels in one of the pivotal studies;

however, there was no clear relationship between serum carbamazepine levels and clinical response, and these were not fixed-concentration studies. Furthermore there were no clear predictors of response when exploratory analyses were done to detect subgroup interactions on the basis of gender, age, race, and national origin. However, there was likely not adequate power to detect such differences.

1.3.3 Safety

Equetra treatment was reasonably safe and well tolerated in the short-term, acute controlled mania studies. The safety and tolerability profile of Equetra treatment in acutely manic subjects was quite similar to that of extended- and immediate-release carbamazepine formulations used in the treatment of other illnesses. There were no new or unexpected adverse events reported. There were no deaths, and there is no indication that Equetra treatment was associated with an increased risk of suicidality or self-injurious behavior. There were relatively few serious adverse events that could be reasonably attributed to Equetra treatment. One subject developed fever and maculopapular rash, which was probably related to Equetra treatment. In the Equetra group, 11% of subjects discontinued due to an adverse event, compared to 5% in the placebo group. In several cases, the adverse event was probably related to treatment with Equetra. These included dizziness, ataxia, nystagmus, asthenia, somnolence, diplopia, rash, pruritus, abnormal liver function tests, nausea, and vomiting.

Commonly reported adverse events (reported in > 5% of the Equetra group and twice the proportion of the placebo group) that were likely due to Equetra treatment were similar to those previously reported during the pre- and post-marketing use of carbamazepine formulations. These adverse events occurred primarily in the central nervous system, digestive system, and skin. The AE include dizziness (44% vs. 12% in the placebo group) somnolence (32% vs. 13%), ataxia (15% vs. 0.4%), speech disorder (6% vs. 0.4%), amblyopia (6% vs. 2%), nausea (29% vs. 10%), vomiting (18% vs. 3%), dyspepsia (15% vs.8%), constipation (10% vs. 5%), dry mouth 6% vs. 1%), pruritus (8% vs.2%), and rash (7% vs. 4%). Less commonly reported adverse events (reported in $\geq$ 2% of the Equetra group and twice the proportion of the placebo group) that can reasonably be attributed to Equetra treatment include tremor, vertigo, cognitive abnormality, paresthesia, twitching, and hypertension. All of these adverse events are included in labeling of carbamazepine products. In managing such adverse events, the clinician should consider such factors as Equetra dose, rate of Equetra titration, serum carbamazepine concentrations, and potential drug-drug interactions.
There were no significant treatment effects of Equetra on pulse and sitting blood pressure parameters. A mean increase in weight of 2.2 pounds from baseline to Day 21 occurred in the Equetra treatment group, versus a mean increase of 0.1 pound in the placebo group. Although the difference between groups was statistically significant, it is probably not clinically significant in the short term. However, Equetra treatment was associated with increases in cholesterol and LDL concentrations, which could be clinically significant. Equetra treatment was associated with an increase in liver function test abnormalities. It was also associated with decreases in hematological parameters (RBC, WBC, hematocrit, hemoglobin, MCH, reticulocytes, basophils, and MCV), that are known to occur with carbamazepine treatment. While these effects were

small and did not appear to be clinically significant in the short-term studies (21 days), such abnormalities would need to be monitored closely during long-term treatment with Equetra. There were no clinically significant Equetra treatment effects on any ECG parameters. In particular, there was no prolongation of the QT or QTcB intervals.

1.3.4 Dosing Regimen and Administration

The dose range and titration rate of Equetra selected in the clinical studies were based on: 1) The recommended dosing regimen of carbamazepine currently prescribed for the treatment of epilepsy (400 mg to 1600 mg daily) and for the treatment of trigeminal neuralgia (200 mg to 1200 mg daily); and 2) data from published studies in Bipolar Disorder.

For the treatment of acute mania, the recommended initial dose of Equetra is 400 mg/day given in divided doses, twice daily. The sponsor proposes that the dose should be adjusted in 200 mg daily increments, up to 1600 mg per day, in order to achieve optimal clinical response. Doses higher than 1600mg/day have not been studied. Monitoring of blood levels is useful, as there appears to be a therapeutic window for serum carbamazepine levels (4-12 ug/mL) benefit.

1.3.5 Drug-Drug Interactions

1.3.5.1 Agents that may affect carbamazepine plasma levels

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, and valproate.

CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include: cisplatin, doxorubicin, felbamate, rifampin, phenobarbital, phenytoin, primidone, and theophylline

1.3.5.2 Effect of carbamazepine on plasma levels of concomitant agents

Carbamazepine treatment increases serum levels of clomipramine, phenytoin and primidone. Bipotrol induces hepatic CYP activity. Equetra would be expected to cause decreased serum levels of the following drugs: acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, and warfarin. The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives, and their reliability may be adversely affected.

1.3.6 Special Populations

Hepatic Dysfunction: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that the liver primarily metabolizes carbamazepine, it would be prudent to proceed with caution during Equetra treatment in patients with hepatic dysfunction.

Renal Dysfunction: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender: No differences in the mean AUC and C max of carbamazepine and carbamazepine-10,11-epoxide were found between males and females.

Pediatrics:
The safety of carbamazepine in children with epilepsy has been studied for up to 6 months. No longer-term data from clinical trials is available. Generally, carbamazepine use in children appeared to be reasonably safe and effective when treating epilepsy.

Pregnancy, Labor & Delivery, Breastfeeding
Carbamazepine can cause fetal harm when administered to a pregnant woman. This finding is included in the sponsor's labeling in the WARNINGS section. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician should carefully weigh the potential benefits of therapy against the risks in treating women of childbearing potential. If Equetra is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. The effect of carbamazepine on human labor and delivery is unknown.

Carbamazepine and its epoxide metabolite are transferred to breast milk during lactation. The serum concentrations of carbamazepine and its epoxide metabolite in the neonate or infant are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions from carbamazepine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age. No systematic studies in geriatric patients have been conducted.

Race: No information is available on the effect of race on the pharmacokinetics of carbamazepine.

CLINICAL REVIEW

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

The sponsor has submitted a New Drug Application for Equetra (carbamazepine extended-release capsules). Carbatrol (the same formulation as Equetra) has been approved for the treatment of epilepsy and trigeminal neuralgia (NDA 20-712). The immediate-release (Tegretol) and extended-release formulations of carbamazepine (Carbatrol) are categorized as anticonvulsant medications. Equetra is a multi-component capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of Equetra. Inactive ingredients include citric acid, colloidal silicon dioxide, lactose

monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate and other ingredients.

The sponsor seeks an indication for Equetra monotherapy in the acute treatment of manic or mixed episodes associated with Bipolar Disorder in adult patients (≥ 18 years of age). The sponsor proposes the trade name, Equetra ™ for carbamazepine extended-release formulation in the acute treatment of mania. The recommended initial dose of Equetra is 400 mg/day, given in divided doses twice daily. The proposed stable dosing range is 400 mg to 1600 mg/day, given in divided doses, twice daily. The drug would be available as 100 mg, 200 mg, and 300 mg capsules.

2.2 Currently Available Treatment for Mania Associated with Bipolar Disorder

Several drugs have been approved for the acute treatment of mania in adults with Bipolar Disorder. These include lithium, valproate, and the atypical antipsychotic drugs, olanzapine, risperidone, quetiapine, and ziprasidone.

2.3 Availability of Proposed Active Ingredient in the United States

Equetra would be readily available in the U.S. if the drug were approved.

2.4 Presubmission Regulatory Activity

On November 1, 2001, the Division met with the sponsor to discuss the submission of the NDA. The Division and the sponsor agreed that two positive, adequate, well-controlled efficacy trials would be sufficient to support a labeling claim for Equetra in the acute treatment of manic episodes associated with Bipolar Disorder. The Division and the sponsor discussed general plans for longer-term trials in mania to study long term efficacy and safety of Equetra. The sponsor agreed to do so as a Phase 4 commitment. Such a trial would be a randomized, placebo-controlled, randomized withdrawal study. The sponsor also agreed to submit post-marketing adverse events reports for carbamazepine extended-release.

3 Significant Findings from Other Review Disciplines

3.1 Statistics

The statistical reviewer, Dr. Ohidul Siddiqui performed an efficacy analysis, and he replicated the sponsor's results. Both pivotal studies were positive for the primary analysis (comparison between treatment groups of changes in mean YMRS at Day 21). Details will be discussed in the Integrated Review of Efficacy section.

3.2 The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

The OCPB reviewers concluded that a number of the sponsor's proposed labeling items are not acceptable. The OCPB reviewers have edited and reorganized a number of sections of the proposed labeling, including the drug interaction section. For example, the labeling for drug interactions for zonisamide, cisplastin, doxorubicin, methsuximide, and phensuximide should be moved to the Precautions section of the label, since the reported interaction for cisplastin and doxorubicin are absorption related, and there are conflicting literature reports regarding zonisamide, methsuximide, and phensuximide.

3.3 Division of Scientific Investigation (DSI)

There were no DSI findings that would significantly alter the outcome or analyses of the studies. There were a relatively small number of protocol violations and drug accountability problems at the sites investigated. For details, please refer to the DSI review completed by Ni Khin, M.D. Dr. Khin concluded that, overall, the data appeared acceptable.

3.4 CMC

The CMC reviewers do not have any particular concerns or recommendations regarding the Bipotrol submission.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The sources of data include the individual study reports, the integrated reviews of efficacy and safety, data sets I JMP files, and the summary of postmarketing experience. Refer to Table 4.2 below for a description of the placebo-controlled trials.

4.2 Table of Clinical Placebo-Controlled Studies

STUDY NUMBER	**105.301** **PIVOTAL TRIAL**	**417.304** **PIVOTAL TRIAL**	**105.302** **LITHIUM NON-RESPONSERS**
Study dates	12-17-99 to 6-18-01	7-23-02 to 4-1-03	1-20-00 to 11-5-01
Sites	27 U.S. sites; 15 states	25 Sites; 19 in U.S and 6 in India	10 U.S. sites
Primary Objective	To assess the efficacy of Equetra in the acute treatment of manic or mixed episodes assoc. w/ Bipolar I Disorder	Identical to that of Study 105.301	Identical to that of Study 105.301
Subjects	Bipolar I Disorder, Manic or Mixed **N=204** Equetra: 101; Placebo:103	Bipolar I Disorder, Manic or Mixed **N=239** Equetra: 122; Plac: 117	Lithium non-responders; Bipolar I Disorder, Manic or Mixed **N=59** Equetra: 29; Placebo: 30
Design	Randomized, double blind, placebo-controlled, flexible-dose, monotherapy 3-week trial.	The design was identical To that of Study 105.301	The design was identical To that of Study 105.301, except for the subject

	Initial Equetra dose: 400 mg/day (200 mg BID). On Day 2, the daily dosage was increased by 200 mg/day to a maximum daily dosage of 1600 mg/day (divided BID) of Bipotrol or placebo.		inclusion criterion above
Disposition	Lead-in phase: 267 subjects Randomized: 204 (EQU- 101; PLA- 103) Completed: EQU- 50% Plac- 45% Discontinued: EQU - 50% Plac- 55%	Lead-in: 319 subjects Randomized: 239 (EQU- 122; Pla- 117) Completed: EQU - 66% Pla- 55% Discontinued: EQU - 34% Pla- 45%	Lead-in: 62 subjects Randomized: EQU -29; Pla- 30 Completed: EQU - 45% Pla- 63% Discontinued: EQU - 55% Pla- 37%
Efficacy results	Baseline YMRS: EQU - 26.6; PLA- 27.3 Endpt. YMRS: EQU - 17.9; PLA- 22.1 Mean Change: EQU - −8.7; PLA- −5.2 P-value: p= 0.0331	Base. YMRS: EQU - 28.5 PLA 27.9 Endpt. YMRS: EQU -13.4 PLA- 20.8 Mean Change: EQU - −15.1 PLA- −7.1 P-value: p< 0.0001	Baseline YMRS: EQU - 30.3 PLA- 28.8 Endpt. YMRS: EQU - 21.4 PLA- 20.1 Mean Change: EQU - −8.9 PLA − 8.7 P-value: p = 0.97

Extension Study 105.303
The table describing extension Study 105.303 is in **Appendix 10.1**.

4.3 Review Strategy

For the efficacy review, I focused on the two pivotal trials. I reviewed the sponsor's Integrated Summary of Efficacy, Study Reports, figures and tables, and the FDA statistical reviewer's review. For the review of safety, I reviewed the Integrated Summary of Safety, Study Reports, figures, tables, and data sets in JMP files for all four trials. I also reviewed the sponsor's safety update and literature review.

4.4 Data Quality and Integrity

The quality and integrity of the submission are acceptable.

4.5 Compliance with Good Clinical Practices

It appears that the trials were conducted in compliance with good clinical practice.

4.6 Financial Disclosures

The sponsor submitted the appropriate documentation regarding financial disclosures (Form OMB No. 0910-0395; Form FDA 3454). There is no indication that any of the investigators had significant conflict of interest.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Taken every 12 hours, carbamazepine extended-release capsules provide steady state plasma levels comparable to immediate-release carbamazepine tablets given every 6 hours, when administered at the same total mg daily dose. Following a single 200-mg oral dose of extended-release carbamazepine, Cmax was 1.9 ± 0.3 μg/mL and Tmax was 19 ± 7 hours. Following chronic administration (800 mg every 12 hours), Cmax was 11.0 ± 2.5 μg/mL and Tmax was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single-dose range of 200-800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. Following a single extended-release dose of carbamazepine, the average half-life range from 35-40 hours and 12-17 hours on repeated dosing. The apparent oral clearance following a single dose was 25 ± 5 mL/min and following multiple dosing was 80 ± 30 mL/min.

After oral administration of 14 C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine.

Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200-mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 μg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of an extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 μg/mL and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and C max of carbamazepine-10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C max of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 μg.hr/mL and 1.5 μg/mL at 800 mg/day to 32.6 μg.hr/mL and 3.2 μg/mL at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Carbamazepine-10,11-epoxide: Carbamazepine-10,11-epoxide is an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 μg/mL and the time to reach the peak was 36 ± 6 hours. Following chronic administration of a extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 μg/mL and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200-800 mg) the AUC and C max of carbamazepine-10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and C max of carbamazepine-10,11-epoxide were dose related, ranging from 15.7 μg.hr/mL and 1.5 μg/mL at 800 mg/day to 32.6 μg.hr/mL and 3.2 μg/mL at 1600 mg/day, respectively, and were less than 30% of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect: A high fat meal diet increased the rate of absorption of a single 400 mg dose (mean T max was reduced from 24 hours, in the fasting state, to 14 hours and C max increased from 3.2 to 4.3 μg/mL) but not the extent (AUC) of absorption. The elimination half-life remains unchanged between fed and fasting state. The multiple dose study conducted in the fed state showed that the steady-state C max values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

5.2 Pharmacodynamics

The mechanism of action of Equetra in mania has not been determined. Carbamazepine has anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Carbamazepine greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Carbamazepine is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

The principal metabolite of carbamazepine, carbamazepine-10,11-epoxide, has anticonvulsant activity, as demonstrated in several in vivo animal models of seizures. Though clinical activity for the epoxide has been postulated, the significance of its activity with respect to the safety and efficacy of carbamazepine has not been established.

5.3 Exposure-Response Relationships

The generally accepted therapeutic range for carbamazepine in the treatment of mania is 4-12 μg/mL. Carbamazepine serum levels were obtained in one of the pivotal studies (105.301). The levels in subjects were generally in the targeted therapeutic range; however, some serum concentrations were as high as 16 μg/mL. There was no clear relationship between the serum

carbamazepine levels and efficacy. Since these were not fixed-dose or fixed-concentration studies, it would be extremely difficult to draw conclusions about potential exposure-response or dose-response relationships.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication is the treatment of acute mania associated with Bipolar Disorder in adults.

6.2 Methods

A full efficacy analysis was conducted for the two pivotal trials. Some efficacy variables were reviewed for the two non-pivotal trials. Sources of information included the Integrated Summary of Efficacy, individual study reports, and tables and figures provided by the sponsor.

6.3 Study Design

6.3.1 Study Sites.

For Study105.301, subjects were enrolled at 27 U.S. sites and randomized to treatment at 24 of these sites. For Study 417.304, subjects were enrolled at 25 clinical study sites. There were 19 sites in the U.S. and 6 sites in India.

6.3.2 Objectives

Pivotal Studies 105.301 and 417.304: the primary objective in each of these studies was to assess the efficacy and safety and of Equetra, compared to placebo, in the acute treatment of manic or mixed symptoms in subjects with Bipolar I Disorder, as measured by the Young Mania Rating Scale (YMRS).

6.3.3 Study Populations

The subject selection criteria were identical for the pivotal studies 105.301 and 417.304.
The key inclusion and exclusion criteria are specified below.

6.3.3.1 Inclusion Criteria

1. Male or female subjects at least 18 years of age
2. Meets DSM-IV criteria for Bipolar I Disorder, Manic Episode or Mixed Episode
3. Has score $\geq$ 20 on YMRS at screening and baseline
4. Female subjects must not be pregnant or breastfeeding. Female subjects of childbearing potential must use a reliable method of contraception

6.3.3.2 Exclusion Criteria

1. Known or suspected hypersensitivity or serious adverse reaction to carbamazepine,

2. carbamazepine products or tricyclic antidepressants; or severe drug allergies or hypersensitivities.
3. History of or clinically significant hepatic, renal, or cardiovascular disease.
4. History of bone marrow suppression.
5. Myocardial infarction within 6 months of beginning the study.
6. History of seizure disorder other than a single childhood febrile seizure.
7. Women who are pregnant or breastfeeding
8. A primary Axis I disorder other than Bipolar Disorder

9. The sponsor has appropriately specified numerous other medical and psychiatric disorders as exclusion criteria.

6.3.4 Trial Design

The three acute monotherapy treatment trials had the identical design. The trials were randomized, double blind, placebo-controlled, parallel group, flexible-dose, multicenter, 3-week trials. Following a placebo lead-in/washout period of 2-5 days, subjects were randomly assigned, in a 1:1 ratio, to receive treatment with either Equetra or placebo for the 3-week double-blind period. All subjects were hospitalized during the lead-in phase and for at least the first 7 days of the treatment phase. After Day 7, subjects could be discharged and administered study treatment as outpatients if, in the opinion of the investigator, the subject demonstrated an adequate response and was clinically stable.

The initial dose of Equetra was 400 mg/day, given as divided doses, twice daily. Beginning on Day 2, the total daily dosage was increased by 200 mg daily to a maximum total daily dosage of 1600 mg/day of Equetra or placebo (8 capsules/day). The stable dose range was 400-1600 mg/day, in divided doses, given twice daily. At any time during the trial, the dose of study medication could be reduced (to a minimum of 400 mg/day) if a subject could not tolerate a particular dose. Permitted concomitant medication included lorazepam for the treatment of agitation and sleep disturbance (up to 6 mg/day for the lead-in period; up to 4 mg/day for the first week of study treatment; and up to 2 mg/day for the second week of treatment). Efficacy and safety assessments were performed at screening, at baseline, and on Days 7, 14, and 21.

6.3.5 Efficacy Measures

The primary efficacy endpoint in the controlled trials was the difference between treatment groups (from baseline to Day 21) in the change in mean YMRS score. The YMRS score was assessed at baseline and on Days 7, 14, and 21. The YMRS is an 11-item scale designed to evaluate the severity of the following symptoms associated with the manic state: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech, language disorder or thought disorder, content, disruptive-aggressive behavior, appearance, and insight. The

symptoms are rated on a scale of 0 to 4 points (for 7 items) or 0 to 8 points (for 4 items), with a maximum total score of 60 points. With a history of many years of use, the YMRS has been extensively studied and widely used by researchers and clinicians, and it is the standard measurement employed in clinical studies for investigations of mania.

Secondary efficacy measures were the Clinical Global Impression-Severity (CGI-S) and improvement scores for overall bipolar (CGI-I-BP) illness, Hamilton Rating Scale for Depression (HAM- D) total score, HAM- D depressed mood item score, YMRS number of responders and sustained responders, and time- to- outpatient status. On the YMRS scale, a subject whose total score decreased by 50% or more from the baseline total score was considered a responder.

6.3.6 Efficacy Findings and Relevant Variables

6.3.6.1 Patient Disposition and Reasons for Discontinuation

Relevant data are presented in the table below. The pattern of disposition and reasons for discontinuation resemble those of other antipsychotic trials in acute mania. Before Day 21, 41% of the Equetra group and 50% of the placebo group discontinued from the study. In both groups, the most common reasons for discontinuation were "Subject Choice" and Lack of Efficacy. Approximately 11% of the Bipotrol group and 5% of the placebo group discontinued due to adverse events.

We requested additional information from the sponsor about discontinuations categorized as "Subject Choice." For the purpose of the Bipolar trials "subject choice" and "withdrew consent" were interchangeable terms. The sponsor stated that data handling guidelines specified that comments must be provided if "adverse event", "protocol violation", or "other" was chosen as the reason for discontinuation. Sites were not required to include any comments or additional details for patients who discontinued due to "subject choice" or "withdrew consent."

The sponsor states that steps were taken during data review to ensure subjects with adverse experiences (AEs) leading to discontinuation were not captured as "subject choice" or "withdrew consent". Any AEs with an action taken listed as "study drug discontinued" were cross-checked with responses on the End of Study (EOS) CRF page. If the EOS page stated that subject withdrew due to "subject choice", then a query was sent to the site to ensure an AE was not the cause for subject discontinuation.

Discontinuations due to lack of efficacy were not investigated during data review.
It was left to the investigator to determine whether the subject withdrew due to lack of therapeutic benefit. Furthermore, it was at the discretion of the investigator to withdraw a subject if the investigator judged that the subject was not receiving any therapeutic benefit. Such terminations were captured as "lack of efficacy".

The tables illustrating the disposition and reasons for discontinuations are in **Appendices 10.2.1 and 10.2.2.**

Studies 105.301 and 417.304- Disposition and Reasons for Discontinuation

	STUDY 105.301		STUDY 417.304		TOTAL	
	Equetra	**Placebo**	**Equetra**	**Placebo**	**Equetra**	**Placebo**
No. of subjects randomized	101	103	122	117	223	220
No. ITT subjects	94 (94%)	98 (95%)	120 (98%)	115 (98%)	214 (96%)	213 (97%)
No. of subjects completed	50 (50%)	46 (45%)	80 (66%)	64 (55%)	130 (58%)	110 (50%)
No. of subjects discontinued	51(50%)	57 (55%)	42 (34%)	53 (45%)	93 (42%)	110 (50%)
Reasons for discontinuation						
Subject choice	17 (17%)	19 (18%)	11 (9%)	11 (9%)	28 (13%)	30 (14%)
Lack of efficacy	14 (14%)	22 (21%)	8 (7%)	27 (23%)	22 (10%)	49 (22%)
Adverse event	13 (13%)	6 (6%)	11 (9%)	6 (5%)	24 (11%)	12 (5%)
Lost to follow-up	3 (3%)	3 (3%)	2 (2%)	2 (2%)	5 (2%)	5 (2%)
Other	3 (3%)	5 (5%)	1 (1%)	3 (3%)	4 (2%)	8 (4%)
Protocol violation	1 (1%)	2 (2%)	9 (7%)	4 (4%)	10 (4%)	6 (3%)

6.3.6.2 Baseline Demographics

In the pivotal trials, 21% of subjects were from India, and 79% were from the U.S. There were no significant differences between treatment groups. Approximately 58% of subjects were White, 21% were Other (from India), 15% were Black, 3% were Latino, 1% were Asian/Pacific Islander, and 0.25% were Native American. There were no significant differences in ethnicity between the treatment groups. Approximately 62% of subjects were male, and 38% were female, distributed evenly between treatment groups. The mean age was 37 in both treatment groups. Approximately 25% of subjects were in the 18-29 age group, 32% were in the 30-39 age group, and 42% were in the age group ≥ 40. The proportions of subjects in each age group were distributed evenly between the treatment groups. Mean weights were quite similar between treatment groups. Thus, the baseline demographic features of subjects as baseline were quite similar. For details, please refer to the table in **Appendix 10.3**.

6.3.6.3 Baseline Severity of Illness and Other Features of Illness

In Study 105.31, the baseline mean YMRS score in the Equetra group was 26.6, and the mean score in the placebo group was 27.3. In Study 417.304, the baseline mean YMRS score in the Equetra group was 28.5, and the score in the placebo group was 27.9. For the combined pivotal studies, 74% of subjects experienced a manic episode, and 36% of subjects experienced a mixed episode at baseline. There was an even distribution of manic and mixed subjects between treatment groups. For duration of illness since first episode, both groups had a mean duration of 7.56 years. Thus, the treatment groups were well matched, except for the lower mean YMRS score in the placebo group in Study 417.304.

6.3.7 Exposure to Equetra by Dose and Duration in the Pivotal Studies

The table below illustrates the Equetra exposure in person-years and by dose range.
For the pivotal studies combined, the most frequent exposures were in the dose range of 800-1000 mg/day. The next most common dose range was 400-600 mg/day, followed by 1200-1400 mg/day, and then 1600 mg/day. The total exposure in the two pivotal trials combined was 9.82 person-years. (For details, refer to **Appendix 10.4.2**.)

EQUETRA EXPOSURE ACCORDING TO DAILY DOSE AND DURATION OF THERAPY IN PIVOTAL STUDIES

	Bipotrol Daily Dose (mg/day)					
Drug Exposure (Years)	200	400-600	800-1000	1200-1400	1600	Total Bipotrol Exposure
Study 105.301)						
N	6	99	90	62	35	101
Sum (Person Years)	0.02	1.1	1.35	0.83	0.75	4.03
Study 417.304						
N	12	120	107	77	47	122
Sum (Person Years)	0.04	1.61	1.98	1.21	0.94	5.79

Mean and Median Daily Equetra Doses for the Pivotal Studies

The table in **Appendix 10.4.3** presents summary statistics for the mean and median final daily Equetra dose taken by subjects during controlled trials 105.301 and 417.304. Subjects randomized to receive placebo were excluded from this analysis. Subjects in the combined controlled protocols took a final mean Equetra dose of 853.4 mg and a median dose of 800mg. Subjects in Protocol 105.301 took a final mean daily dose of 952.5mg and a median dose of 800mg. Subjects in Protocol 417.304 took a final mean daily dose of 726.2mg and a median dose of 600mg. Subjects in the non-pivotal failed trial (105.302) took a final mean daily dose of 1050 mg and a median dose of 1100 mg. .

6.3.8 Serum Carbamazepine Concentrations and Clinical Response

Serum carbamazepine concentrations were measured in Study105.301. Blood samples were obtained on Days 7, 14, and 21 or at early termination. The mean serum carbamazepine concentrations in Bipotrol-treated patients were 11.5 μg/mL, 10.1 μg/mL, 8.7 μg/mL, and 8.9 μg/mL on Days 7, 14, 21, and at endpoint, respectively, during the double-blind treatment period. The mean serum carbamazepine concentrations at each study visit and endpoint during double-blind treatment showed no statistically significant association with YMRS score at any time point. This was not a fixed-dose study or a study designed to assess a possible dose-response or concentration-response relationships. Thus, there are limitations in interpreting the serum carbamazepine concentration data. However, the concentration data indicate that, in general, most subjects had serum carbamazepine concentrations that are considered to be in the therapeutic range (4-12 ug/mL).

6.3.9 Concomitant Medications Used During the Trials

In both treatment groups, a relatively small proportion of subjects used concomitant medications of any kind during the controlled trials. Similarly, relatively few subjects used concomitant psychotropic medications that were prohibited by protocol. Other than lorazepam permitted by protocol, 0.4% of subjects in each treatment group used benzodiazepines; 0.4% of subjects in each group used antipsychotic medications; and 0.4% of the Equetra group used lithium. The number of doses and the total dosages were not provided. It is very unlikely that the use of prohibited psychotropic medications had an effect on the outcome of the trials.

6.3.10 Lorazepam Usage in the Trials

Lorazepam was allowed at doses of up to 6 mg/day during the screening period, to treat agitation and sleep disturbances. Lorazepam dosages up to 4 mg/day during the first week of double-blind treatment were permitted. During the second week of double-blind treatment, lorazepam treatment was limited to 2 mg/day

It is unlikely that the use of lorazepam in either treatment group had an effect on the outcome of the studies, since the lorazepam exposure in the two groups appears similar. In the Equetra group, 185 (74%) of subjects used lorazepam as permitted by the protocol. Similarly, 185 (75%) of the placebo subjects used lorazepam. For Study 105.301, the dosages of lorazepam were available for only 50% of subjects receiving lorazepam. For these subjects, the mean daily dose of lorazepam was 7.8 mg and 5.8 mg in the Equetra and placebo group, respectively. The mean duration of lorazepam use was 8.2 and 8.8 days in the Equetra and placebo group, respectively. In Study 417.304, the mean daily dose of lorazepam was 6.4 mg and 7.7 mg for the Equetra and placebo group, respectively. The mean duration of lorazepam use was 7.9 days and 9.0 days for the Equetra and placebo group, respectively.

6.3.11 Efficacy Findings

6.3.11.1. Statistical Analysis Plan

The primary efficacy endpoint was the change in mean YMRS score at the end of double-blind treatment period analyzed for the LOCF data of the ITT population using the analysis of covariance (ANCOVA) model. The model included treatment group, the corresponding baseline score (the covariate), and site. In an exploratory analysis, the treatment effect by site was

examined by including the site- by- treatment interaction in the ANCOVA model. The primary efficacy endpoint was also analyzed based on the sub- group populations: gender (males vs. females), subjects of various age groups, and ethnic origin.

The key secondary efficacy measure was the CGI-Severity score at the endpoint, analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and site as the main factors and the baseline value as the covariate for the ITT population. The CGI score was analyzed using the Chi-square test with continuity adjustment.

6.3.11.2. Sponsor's Primary Analysis Results

Details are presented in the table below. In Study 105.301, the change in mean YMRS score was − 8.7 in the Equetra group and − 5.12 in the placebo group. The difference (−3.53) was statistically significant (p=0.0331), in favor of Equetra treatment. In Study 417.304, the change in mean YMRS score was −15.08 in the Equetra group and −7.11. The difference (−7.97) was statistically significant (p<0.0001), in favor of Equetra treatment. In the analysis of the pooled YMRS data, there was a statistically significant difference (p<0.0001). Currently, it is not clear why the estimated treatment effect of Equetra in Study 417.304 was considerably larger than the estimated treatment effect in Study 105.301. Possibilities include differences in patient population, severity of illness, dose, serum concentration, length of hospital stay, regional differences, etc. However, the study was not designed to analyze the effect of these variables on treatment response.

Primary Efficacy Endpoint: Change in Mean YMRS Scores in the Pivotal Trials

STUDY	EQUETRA				PLACEBO					
	N	YMRS Baseline	YMRS Endpoint	Change	N	YMRS Baseline	YMRS Endpoint	Change	Diff	p-value
105.301	94	25.6	17.9	-8.7	98	27.3	22.1	-5.2	-3.5	0.0331
417.304	120	28.5	13.4	-15.1	115	27.9	20.1	-7.1	-8.0	<0.0001
Pooled Data	214	27.6	15.4	-12.3	213	27.6	21.4	-6.2	-6.1	<0.0001

6.3.11.3 FDA Statistics Reviewer's Data Analysis Results

The statistics reviewer re-analyzed the data sets of studies 105.301 and 417.304 according to the protocol-specified statistical analysis plans, an LOCF analysis. The reviewer replicated the sponsor's findings for the primary and secondary efficacy measures. The table below illustrates the primary efficacy results of the studies 105.301 and 417.304 based on the primary efficacy measure (the change from baseline to endpoint in mean YMRS score). In both studies, there was a statistically significant difference in change of mean YMRS scores at endpoint between the treatment groups (in favor of Equetra). In Study 105.301, the least square mean changes from baseline to endpoint in YMRS scores were −7.82 in the Equetra group and −4.77 in the placebo group. There was a statistically significant difference between groups (−3.05; p = 0.033). In Study 417.304, the least square mean changes from baseline to endpoint in mean YMRS scores were −14.83 in the Equetra treatment group and −6.96 in the placebo group. The difference between treatment groups was statistically significant (−7.87; p <0.0001).

Table 1: LOCF Analyses of Covariance of the change in mean YMRS score

	LEAST SQUARES			
	Mean Change	SE	Mean Difference from placebo	P-value
Study #105.301				
Placebo (n=98)	-4.77	1.19		
Equetra (n=94)	-7.82	1.18	-3.05	0.033
Study #417.304				
Placebo (n=115)	-6.96	1.09		
Equetra (n=120)	-14.83	1.05	-7.87	<0.0001

LS mean and P-values are based on ANCOVA model with baseline (covariate), site, and treatment group in the model for post-randomization visits.
*Sponsor did not report the least square means. The statistics reviewer produced the LS means using the above ANCOVA model. The sponsor's reported P-values are matched with the reviewer's calculated P-values.

Table 2 illustrates the primary efficacy results of studies 105.301 and 417.304 based on the primary efficacy measure (the change in mean YMRS score from baseline to each treatment week) based for observed cases. Individual study results revealed that in Study 417.304, the differences between the two groups with respect to mean YMRS score were statistically significant at all time points (p<0.0001). In Study 105.301, statistically significant differences between the groups were observed only at Day 21 using the observed case analysis (p=0.016).

Table 2: Mean Change in Weekly YMRS Total Scores in the Subjects with Mixed or Manic Bipolar Disorder in General - ITT Population (Observed Case)

	Study #105.301					Study# 417.304					
Treatment Group	N	Least Square Means	SE	LS Mean Difference from Placebo	p-value	Treatment Group	N	Least Square Means	SE	LS Mean Difference from Placebo	p-value
Day 7						**Day 7**					
Placebo	98	-4.90	.93			Placebo	114	-5.55	.79		
Equetra	94	-6.07	.93	-1.17	0.294	Equetra	120	-9.89	.82	-4.34	<.0001
Day 14						**Day 14**					
Placebo	72	-5.51	1.33			Placebo	95	-8.60	1.09		
Equetra	74	-8.43	1.35	-2.92	0.071	Equetra	103	-14.28	1.05	-5.66	<.0001
Day 21						**Day 21**					
Placebo	51	-7.29	1.46			Placebo	75	-10.36	1.20		
Equetra	52	-11.94	1.57	-4.65	0.016	Equetra	89	-17.14	1.15	-6.78	<.0001

Secondary Efficacy Analyses - Studies 105.301 and 417.304

Table 4 summarizes the LOCF endpoint efficacy results of the key secondary efficacy measure, CGI-severity. The difference between treatment groups in the change of mean CGI-S was statistically significant, in favor of Equetra in each of the studies.

Table 4: LOCF Analyses of Covariance on the Change Scores of the Secondary measures(ITT Population)

Secondary Measures		Least Squares			
		Mean Change	SE	Mean Difference from placebo	P-value
CGI-Severity Scores	**Study #105.301**				
	Placebo (n=98)	-0.241	.137		
	Equetra (n=94)	-0.638	.137	-0.397	0.017
	Study #417.304				
	Placebo (n=115)	-0.468	.137		
	Equetra (n=120)	-1.355	.132	-0.887	<.0001

LS mean and P-values are based on ANCOVA model with baseline (covariate), site, and treatment group in the model for post-randomization visits.
*Sponsor did not report the least square means. This reviewer produced the LS means using the above ANCOVA model. Sponsor's reported P-values are matched with this reviewer's calculated P-values.

SUBGROUP ANALYSES - STUDIES 105.301 AND 417.304

In both of the studies, subgroup analyses of the primary efficacy endpoint (change in mean YMRS scores) were performed to evaluate the uniformity of treatment effect within patient subgroups (gender, age: 18-39 years age vs. ≥ 40 years age, race: Caucasian Vs. Non-Caucasian, and national origin in Study 417.304: US Population Vs. Indian Population). An ANCOVA model that included the subgroup characteristic, treatment group, baseline mean YMRS scores, and a treatment-by-characteristic interaction term was used to test at $p<0.05$, for evidence of a difference in the treatment effect across levels of the subgroup characteristic. No significant interaction effect of treatment group by any of the subgroup characteristics was found. The lack of significant interaction indicates that the treatment effect is similar irrespective of the patients' characteristics.

SUMMARY AND CONCLUSIONS

Using the LOCF analyses, a positive response to Equetra monotherapy was observed at Day 21 for the ITT population in both studies. Subjects treated with Equetra had an improvement in acute manic symptoms as measured by the change in mean in YMRS score from baseline to endpoint. Studies 105.301 and 417.304 demonstrated that Equetra was an effective drug for the treatment of manic symptoms in bipolar patients (manic or mixed) for up to 21 days at a titrated dose of between 200 mg/day and 1600 mg/day, given twice daily.

The estimated size of the Equetra treatment effect was a reduction in mean YMRS score of and 8.0 in studies 105.301 and 417.304, respectively. In my opinion, the size of the Equetra treatment effect was clinically meaningful in both studies; although, the estimated size of the treatment effect was modest in study 105.301. There were no particular predictors of response, as indicated by the results of the subgroup analyses. However, the study was not designed to adequately test for potential subgroup effects on treatment response. Furthermore, it seems reasonable to expect that one could generalize from the results of these trials to the general population of Bipolar Disorder patients experiencing an acute manic episode, since the study population represented well the general population of patients with Bipolar Disorder with acute mania.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods

Adverse events were classified by body system and preferred term according to the COSTART dictionary, Fifth Edition, 1996. In all three controlled studies, safety assessments included adverse events (AEs), vital signs, laboratory tests (hematology, blood chemistry, and urinalysis), and 12-lead electrocardiogram (ECG). Safety assessments were conducted at screening, at baseline prior to dosing, and on Days 3, 7, 14, and 21 (or within 2 days of the subject's last full dose of study drug if the subject discontinued from the study

prematurely).

7.2 Safety Findings

7.2.1 Deaths

There were no deaths in the Bipotrol Bipolar Disorder clinical program.

7.2.2 Suicidality and Self-Injury

In the pivotal trials, there was one case of suicidality in the Equetra group and one case in the placebo group. In the Equetra case, the subject intentionally took an overdose of study medication. It is unclear whether she knew or believed that she was being treated with active drug versus placebo. A 60-year-old white female subject (105.303/036-201) took 36 x300mg and 1x 200mg carbamazepine capsules. The subject was hospitalized. She had a poor responsive state, slurred speech, confusion, and restlessness requiring restraints. The subject's carbamazepine level was 24.6 ug/mL (therapeutic range is 4-12 ug/mL). She was stabilized medically and admitted to a psychiatric hospital unit. It appears unlikely that the suicidal behavior was related to treatment with Equetra.

There was one case of suicidal ideation without suicidal behavior in the placebo group. This was categorized as a serious adverse event, since the subject required re-hospitalization. There were no reports of suicidality in the two non-pivotal studies. Furthermore, there were no adverse events that appeared to constitute self-injury in any of the 4 studies (other than the case of intentional overdose discussed above).

7.2.3 Serious Adverse Events

7.1.3.1 Pivotal Studies (417.304 and 105.301)

There were relatively few serious adverse events in the two pivotal trials. In the Equetra group, 4% of subjects had SAE reported. In the placebo group, 5% of subjects had SAE reported. The majority of SAE (85%) in both treatment groups were acute psychiatric symptoms (e.g., exacerbation of mania, depression, mixed symptoms, or suicidality, which were probably related to the illness under treatment). In the case of fever and maculopapular rash, it is probable that the symptoms were related to treatment with Equetra, as these are known adverse events with carbamazepine treatment. In all other cases, it appears unlikely that the SAEs were related to treatment with Equetra. None of the SAE was new or unexpected adverse events associated with treatment with carbamazepine.

Table. Serious Adverse Events in the Pivotal Trials

SERIOUS ADVERSE EVENT	EQUETRA N= 223	PLACEBO N= 220
Exacerbation of Bipolar Disorder	6	9
Suicidality	1	1
Fever & maculopapular rash	1	0
Orbital fracture	0	1

7.1.3.2 Study 105.302 (Lithium-resistant subjects)
In the Equetra group, one subject (3%) had an SAE (exacerbation of Bipolar Disorder). Similarly, in the placebo group, one subject (3%) had an SAE (exacerbation of Bipolar Disorder).

7.1.3.3 Extension Study 105.303
During the open-label Equetra extension study, 12 (13%) had SAE, all of which were probably related to the illness under study (mania, suicidality, and agitation). It is unlikely that any of these SAE were related to treatment with Equetra.

7.2.4 Discontinuations Due to Adverse Events

7.2.4.1 Pivotal Studies 417 and 301
For the pivotal studies combined, 36 (8%) subjects discontinued from the study due to adverse events. In the Equetra group, 24 (11%) subjects discontinued due to AE. In the placebo group, 12 (5%) subjects discontinued due to AE. In several cases, the AE was probably related to treatment with Equetra (dizziness, ataxia, nystagmus, asthenia, somnolence, and diplopia). The following AE were likely or possibly related to treatment with Equetra: rash, pruritus, febrile illness, abnormal LFTs, nausea, and vomiting. These conclusions are based on: 1) the known, commonly reported AE associated with carbamazepine treatment; and
2) the higher proportions of subjects in the Equetra group (compared to the placebo group) who experienced these adverse events. There were no new or unexpected AE related to treatment with Equetra. For details, please refer to the table in **Appendix 10.5.1.**

7.2.4.2 Study 105.302 (lithium non-responders)
Six (20%) subjects in the Equetra group withdrew from the study due to adverse events. In the placebo group, there were no discontinuations due to adverse events. In four cases, the AE were probably related to treatment with Equetra, based on the known AE profile for carbamazepine treatment (rash, dizziness, vomiting, ataxia, lightheadedness, and generalized weakness). The other two cases were probably related to the illness under treatment (mania and agitation. For details, refer to Table in **Appendix 10.5.2.**

7.2.4.3Extension Study 303
Essentially, no concern, other than RASH in 6% of the previously untreated subjects and 2% of the previously treated subjects. See the table in **Appendix 10.5.3**.

7.2.5 Common Adverse Events

Commonly reported adverse events (reported in > 5% of the Equetra group and twice the proportion of the placebo group) that were likely due to Equetra treatment were similar to those previously reported during the pre- and post-marketing use of carbamazepine formulations. These adverse events occurred primarily in the central nervous system, digestive system, and skin. The AE include dizziness (44% vs. 12%) somnolence (32% vs. 13%), ataxia (15% vs. 0.4%), speech disorder (6% vs. 0.4%), amblyopia (6% vs. 2%), nausea (29% vs. 10%), vomiting (18% vs. 3%), dyspepsia (15% vs.8%), constipation (10% vs. 5%), dry mouth 6% vs. 1%), pruritus (8% vs.2%), and rash (7% vs. 4%). There were no new or unexpected adverse events.

Table. Adverse Events Reported in ≥ 5% of Equetra group and 2X Proportion in Placebo Group

ADVERSE EVENT	EQUETRA N= 251 (%)	PLACEBO N= 248 (%)
Body as a Whole		
Asthenia	8	4
Nervous System		
Dizziness	44	12
Somnolence	32	13
Ataxia	15	0.4
Speech disorder	6	0.4
Amblyopia	6	2
Digestive System		
Nausea	29	10
Vomiting	18	3
Dyspepsia	15	8
Constipation	10	5
Dry mouth	6	1
Skin		
Pruritus	8	2
Rash	7	4

7.2.6 Less Common Adverse Events

Less commonly reported adverse events (reported in ≥ 2% of the Equetra group and twice the proportion of the placebo group) that can reasonably be attributed to Equetra treatment include

tremor, vertigo, cognitive abnormality, paresthesia, and twitching. These are known adverse events attributable to carbamazepine treatment.

Less Common Adverse Events Likely Attributable to Equetra Treatment

AE	EQUETRA	PLACEBO	RELATEDNESS
Hypertension	3%	0.4%	Probable
Paresthesia	2%	1%	Probable
Thinking abnormal	2%	0.4%	Possible
Tremor	3%	1%	Probable
Twitching	2%	1%	Probable
Vertigo	2%	1%	Probable

7.2.7 Laboratory Findings

7.2.7.1 Serum Chemistry Findings

Central Tendencies 7.1
In the 3 short-term controlled studies, there were a number of changes in mean chemistry parameters in the Equetra group that were statistically significant. **Appendix 10.6.1** illustrates the details. The following endpoint values were higher, compared to the placebo group: albumin, alkaline phosphatase, cholesterol, HDL, total bilirubin, total calcium, total protein, and uric acid. Most of these increases are not clinically significant. However, the increases in cholesterol levels (21.5 mg/dL and 0.78 for the Equetra and placebo), respectively, may be clinically significant. Similarly, the LDL increased by 18.9 mg/dL in the Equetra group compared to 5.2 in the placebo group. On the other hand, the HDL increased by 3.7 mg/dL and 0.5 in the Equetra and placebo groups respectively.

Outlier Analysis: There were some significant differences between treatment groups in the number of outliers with increased chemistry values. (Refer to **Appendix 10.6.2**). These differences include cholesterol (30% vs. 11% in the placebo group), direct HDL (5.6% vs. 0), and LDL (20% vs. 9%). Differences occurred for liver function tests as well. The Equetra group had a higher proportion of outliers for alkaline phosphatase (8.6% vs. 5.4%) and for SGPT (10.8% vs. 4.4%). These changes may be clinically significant, depending on the values for an individual subject. One subject (0.4%) discontinued from the study due to an abnormally elevated liver function test result.

7.2.7.2 Hematology Findings

Central Tendency Analysis
For changes in mean hematology parameters, there were several small but statistically significant differences between treatment groups. (Please refer to **Appendix 10.6.3**). Decreases in the Equetra group were observed for RBC, WBC, hematocrit, hemoglobin, MCH, and reticulocytes. In the Equetra group, there were small increases in mean basophils and MCV. The greatest

decrease was observed for WBC (-1.2×10^3 vs. -0.8). The decrease in RBC was -0.054×10 (6^{th} power). Such changes might have been significant for an individual subject; however, other than for the change in WBC, the mean hematologic parameter changes were relatively small.

Outlier Analysis (Appendix 10.6.4)
For several hematology parameters, there were a significantly higher proportion of outliers in the Equetra group compared to the placebo group. In the Equetra group, 2% of subjects had significant decreases in RBC (compared to 1.3% of the placebo group). Similarly, in the Equetra group, 4.6% of subjects had an abnormally low WBC (compared to 1.7% of the placebo group). In addition, the reticulocyte count was decreased in 14.6% of the Equetra group and 5.2% of the control group. Such changes might be clinically significant for an individual subject, depending on the magnitude of the abnormality. No subject discontinued from the study due to an abnormal hematology parameter.

7.2.8 Vital Signs and Weight

Essentially, there were no significant findings. (Refer to **Appendix 10.7**). There were no significant differences between treatment groups and no significant changes in mean vital sign (pulse and sitting blood pressure) parameters in the short-term or long-term studies. A mean increase in weight of 2.2 pounds from baseline to Day 21 occurred in the Equetra treatment group, versus a mean increase of 0.1 pound in the placebo group ($p<0.0001$). This difference is not likely to be clinically significant. The change in mean weight in the long-term Equetra study was a decrease of 1 pound.

7.2.9 Electrocardiograms (ECG) Findings

Central Tendency (Refer to **Appendix 10.8.1**)
There were no clinically significant differences between groups or changes with Equetra treatment in mean ECG parameters. In both treatment groups in the pivotal studies, there was a small change in mean QTcB between endpoint and baseline (-4.6 and $+0.7$ msec in the Equetra and placebo groups, respectively).

Outlier Analysis for Specific ECG Parameters.
The criteria listed in Table 1 were used to provide the outlier analyses for the specified ECG parameters.

Table 1: Outlier Criteria for ECG Parameters

Test	Criteria
Heart Rate	≤ 40 beats/min or ≥ 120 bests/min
PR Interval	≥ 200 msec

QT Interval	≥ 480 msec
QRS Interval	≥ 120 msec
QTc	≥ 500 msec

Appendix 10.8.2 is a listing of all subjects who had normal baseline ECG parameters and an out-of-range value at endpoint. Seven (7) subjects in the short-term Equetra group had out-of-range endpoint values; 6 subjects had PR Interval increases, and 1 subject had decreased ventricular rate. There were no subjects in the short-term Equetra group that met criteria for QRS, QT, or QTcB out-of-range endpoints.

Six (6) subjects in the short-term placebo group had out-of-range endpoint values; 4 subjects had PR Interval increases and 2 subjects had QRS Interval increases. There were no subjects in the short-term placebo group that met criteria for ventricular rate, QT, or QTcB out-of-range endpoints.

Five (5) subjects in the long-term Equetra group had out-of-range endpoint values; 4 subjects had PR Interval increases and 1 subject had QRS Interval increases. There were no subjects in the long-term Equetra group that met criteria for ventricular rate, QT, or QTc out-of-range endpoints.

For heart rate, only 1 subject (0.4%) in the short-term studies on Equetra had a decrease below 40 BPM that had been between 40 and <120 at baseline. There were no other subjects below 40 or above 120 BPM for the short-term placebo groups or long-term Equetra groups. (Refer to **Appendix 10.8.3**)

For PR intervals, 6 subjects (2.5%) in the short-term Equetra group, 4 subjects (4.7%) in the short-term placebo group, and 4 subjects (4.7%) in the long-term Equetra group had PR intervals ≥ 200 msec, with a baseline PR interval < 200 msec. (Refer to **Appendix 10.8.4**).

For the QRS interval, no subjects (0.0%) in the short-term Equetra group, 2 subjects (0.8%) in the short-term placebo group, and 1 subject (1.1%) in the long-term Equetra group had QRS intervals that were ≥ 120 msec, with baseline QRS intervals <120 msec. (Refer to **Appendix 10.8.5**).

For those subjects having end of study ECG, there were no subjects (0.0%) from any treatment group exhibiting QT interval readings ≥ 480 msec, with baseline readings < 480 msec. For those subjects having end of study ECG, there were no subjects (0.0%) from any treatment group exhibiting QTc Bazett readings ≥ 500msec, with baseline readings < 500 msec.

Qualitative changes in QT Interval and QTc Bazett are presented for the short-term trials in Table 7. For QT intervals 6 subjects (2.4%) in the short-term Equetra group and 13 subjects (5.2%) in the placebo group had an increase in QT interval ≥ 60 msec change from baseline to endpoint. For QTc Bazett 5 subjects (2.0%) in the short-term Equetra group and 2 subjects (0.8%) in the placebo group had an increase in QTcB > 60 msec change from baseline to

endpoint. Increases in QTcB of ≥ 30 msec occurred in 6.4% and 12.5% of the Equetra and placebo group, respectively.

In the Equetra group in one of the controlled studies, one subject was discontinued due ECG abnormalities (ST-T change and left bundle branch block). No subject was discontinued from the studies due to a prolongation of the QT or QTcB interval.

Table 2: Qualitative Change in QT Interval and QTc Bazett Recorded in Phase 3 Short-term Studies (105.301, 105.302, and 417.304)

Change from Baseline to Endpoint	Treatment Group	
	Equetra	Placebo
QT Interval (msec)		
Not Available (NA)	33 (13.1%)	40 (16.1%)
< 0	102 (40.6%)	89 (35.9%)
0 - <30	70 (27.9%)	76 (30.6%)
30 - <60	40 (15.9%)	30 (12.1%)
>= 60	6 (2.4%)	13 (5.2%)
Total	251	248
QTc Bazett (msec)		
NA	33 (13.1%)	40 (16.1%)
< 0	115 (45.8%)	100 (40.3%)
0 - <30	82 (32.7%)	75 (30.2%)
30 - <60	16 (6.4%)	31 (12.5%)
>= 60	5 (2.0%)	2 (0.8%)
Total	251	248

Not Available (NA): Records are not available either at baseline or endpoint

7.2.10 Withdrawal Phenomena and Abuse Potential

Withdrawal effects were not studied in the Equetra Bipolar Disorder clinical program. However, because of the anticonvulsant properties of carbamazepine, discontinuation of Equetra should be gradual, in order to prevent seizures. Equetra and other carbamazepine formulations are not known to have abuse potential.

Overdose Experience (Sponsor's Literature Search). The lowest known lethal dose of carbamazepine in adults is >60 g (39-year-old man). The highest known doses survived by an adult were 30 g (31-year-old woman); in children, 10 g (6-year-old boy); and in small children, 5 g (3-year-old girl). Of 52 cases of carbamazepine intoxication reported in the literature since 1966, over 86% (45) were intentional overdoses. Seventy-three percent (38) were non-fatal and subjects recovered without sequelae. Severe mental illness, underlying cardiovascular disease,

and/or multiple drug overdoses, were complicating factors in the majority of cases in which death was reported. To date, no reports of suicide have been associated with beaded, extended-release capsules of carbamazepine.

7.2.11 Postmarketing Experience

Carbamazepine extended-release capsule formulation has been available as Carbatrol® in the U.S. for the treatment of patients with epilepsy and trigeminal neuralgia since 1997. Since then, spontaneous reports of adverse experiences in patients taking Carbatrol have been evaluated, and the literature has been monitored. Shire has updated this evaluation, previously reported in periodic safety reports, for the purposes of this submission. This submission includes:

1. Data from cases in which patients were administered carbamazepine as monotherapy or concomitantly with other drug products.
2. Data from cases in which patients were administered carbamazepine for the treatment of Bipolar Disorder.
3. Data from cases in which patients were administered carbamazepine concomitantly with Lithium.
4. Data from cases in which patients committed or attempted suicide since the possibility of suicide attempt is inherent to Bipolar Disorder.

Since approval, 314 post-marketing adverse events occurring in patients taking Carbatrol have been recorded in Shire's electronic adverse event database. The AE that were reported in more than 5 cases were coded according to MedDRA preferred terms. The data are summarized below.

POST MARKETING AE OCCURRING IN > 5 AGGREGATE CASES		
Event Body System	MedDRA Preferred Term	# Events
Blood and lymphatic system disorders	Leukopenia	6
Gastrointestinal disorders	Nausea	14
	Diarrhea	7
	Vomiting	12
General disorders	Drug ineffective	11
	Pyrexia	10
Nervous system disorders	Convulsion	56
	Dizziness	15
	Headache	10
	Somnolence	9
Psychiatric disorders	Suicide	9
Skin and subcutaneous tissue disorders	Alopecia	9
	Urticaria	43
	Pruritus	10
	Stevens Johnson Syndrome	6

None of the AE was new or unexpected with treatment with Carbatrol. With the exception of "drug ineffective" and "convulsion," the AEs are already included in the proposed Equetra labeling. The sponsor does not plan to include "convulsion" in labeling, since, carbamazepine is indicated for the treatment of epilepsy, and convulsion is commonly the disease under study. However, in the "Warning, Use in Pregnancy" section, the sponsor will include language about the risk of convulsions in seizure patients who undergo abrupt cessation of treatment with carbamazepine.

Post-Marketing Experience with Carbatrol Used in Bipolar Disorder
The sponsor identified 37 unique, pertinent case reports. In all except 5 cases, the reported adverse events had already been listed in labeling. The newly reported adverse events include galactorrhea, dystonia, stiff gait, urinary incontinence, and musculoskeletal stiffness. The sponsor states that in all 5 cases, the AE could be attributable to use of concomitant psychotropic medications.

Literature Review- for Bipolar Disorder
Review of the literature regarding carbamazepine use in Bipolar Disorder suggests that the safety profile in this population is similar to the safety profile when Carbatrol is used in the treatment of epilepsy. Although patient demographics, concomitant medications, and carbamazepine dose differ somewhat, adverse events are most commonly of the CNS, GI, dermatologic, hematologic or metabolic body systems. There were two reports of osteopenia, single case reports of sexual dysfunction (female), sexual dysfunction (female), and drug interaction with risperidone (40% reduction in serum risperidone level).

Carbamazepine and Lithium use in Bipolar Disorder
There are reports of increased neurotoxicity when lithium and carbamazepine are used in combination. This has been specifically described by Chaudhry (35.108), Fawcett (35.107) Ghose, (35.109) and Shukla (35.106) as most commonly including confusion, hyperreflexia, coarse tremors, paresthesia, drowsiness, ataxia and nystagmus. It has been suggested that this is an effect of lithium exacerbating the CNS adverse experience profile inherent with carbamazepine in patients with underlying CNS or metabolic disease, hence the nature of the adverse experience is already described in carbamazepine labeling.

There is one report (Mayan 35.067) of a patient experiencing lithium intoxication following the addition of carbamazepine. This was due to increased plasma lithium concentrations following acute renal failure, which was, ascribed a probable relationship to carbamazepine. Urinalysis was compatible with interstitial nephritis and one reference to a previous case With carbamazepine is cited together with one reference to lithium as a possible causal agent. Carbamazepine was withdrawn and the patient recovered. Acute renal failure is already included in the Carbatrol label.

Important hematological adverse events attributed to the use of carbamazepine use are leukopenia and agranulocytopenia. Conversely, it is recognized that lithium may cause leukocytosis. Three publications (Joffe 35.092, Servant 35.093 and Brewerton 35.095) reported that leukopenia or agranulocytopenia associated with use of carbamazepine was reversed by combination therapy with lithium.

Adequacy of Patient Exposure and Safety Assessments

7.2.12 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Exposure (Appendix 10.4.1)
In the Equetra Mania program, 299 subjects were exposed to Equetra for a total of 31.7 person-years. In the three short-term, double blind, placebo controlled s studies, 251 subjects were exposed to Equetra for a total exposure of 10.9 person years. Of the 92 subjects in the open-label extension trial, 48 were newly exposed to Equetra, as they had been treated with placebo during the double-blind phase. The total Equetra exposure in the long-term open-label study was 20.8 person-years.

ADDITIONAL CLINICAL ISSUES

Dosing Regimen and Administration

The dose range and titration rate of Equetra selected in the clinical studies were based on: 1) The recommended dosing regimen of carbamazepine, currently prescribed for the treatment of epilepsy at doses of 400 mg to 1600 mg daily and for the treatment of trigeminal neuralgia at doses of 200 mg to 1200 mg daily; and 2) data from previous published studies in Bipolar Disorder.

For the treatment of acute mania, the recommended initial dose of Equetra is 400 mg/day given in divided doses, twice daily. The dose should be adjusted in 200 mg daily increments to achieve optimal clinical response. Doses higher than 1600mg/day have not been studied. Monitoring of blood levels of carbamazepine is useful, as there appears to be a therapeutic window for serum carbamazepine levels (4-12 ug/mL), above which toxicity is common without clear benefit.

Drug-Drug Interactions

Agents that may affect carbamazepine plasma levels
CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include cimetidine, danazol, diltiazem, macrolides, erythromycin,

troleandomycin, clarithromycin, fluoxetine, loratadine, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketoconazole, itraconazole, verapamil, and valproate.

CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include: cisplatin, doxorubicin HCL, felbamate, rifampin, phenobarbital, phenytoin, primidone, and theophylline

Effect of carbamazepine on plasma levels of concomitant agents
Carbatrol increases levels of clomipramine, phenytoin and primidone. Carbatrol induces hepatic CYP activity. Carbatrol causes, or would be expected to cause decreased levels of the following: acetaminophen, alprazolam, clonazepam, clozapine, dicumarol, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phensuximide, phenytoin, theophylline, valproate, and warfarin. The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Special Populations

Hepatic Dysfunction: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. However, given that carbamazepine is primarily metabolized in the liver, it is prudent to proceed with caution in patients with hepatic dysfunction.

Renal Dysfunction: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Gender: No difference in the mean AUC and C max of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

Pediatrics:
The safety of carbamazepine in children with epilepsy has been studied for up to 6 months. No longer-term data from clinical trials is available. Generally, carbamazepine use in children with epilepsy appears to be reasonably safe and effective.

Pregnancy, Labor & Delivery, Breastfeeding
Carbamazepine can cause fetal harm when administered to a pregnant woman. This finding is included in the sponsor's labeling in the WARNINGS section.

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician should weigh the benefits of therapy against the risks in treating or counseling women

of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The effect of carbamazepine on human labor and delivery is unknown.

Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age. No systematic studies in geriatric patients have been conducted.

Race: No information is available on the effect of race on the pharmacokinetics of carbamazepine.

Postmarketing Risk Management Plan

OVERALL ASSESSMENT

Conclusions

The results of two adequate and well-controlled trials of Equetra monotherapy in the acute treatment of mania demonstrate that the drug is efficacious for up to 21 days of treatment. The estimated size of the treatment effect appears to be clinically significant. There were no clear predictors of response. Moreover, it seems reasonable that one can generalize from these results to the general population of Bipolar Disorder, Manic patients, since the study population well represented the general population of Bipolar Disorder patients.

Acute Equetra treatment in Bipolar Disorder, Manic subjects was reasonably safe and well tolerated, although a high proportion of subjects treated with Equetra developed adverse effects in the central nervous system. Such adverse events may be manageable by considering the dose, serum concentration, rate of titration, and potential drug-drug interactions. Other known and potentially serious adverse events occurred in the trials. These included rash and decreases in hematologic parameters (RBC, WBC, hematocrit, hemoglobin, MCH, and reticulocyte count. The clinician should regularly monitor hematologic parameters as well as liver function tests. There is some evidence that patients who develop rash may be more likely than others to develop hematologic abnormalities. Therefore, they should be monitored closely.

Recommendation on Regulatory Action

I recommend that the Division take an approvable action for Equetra as monotherapy in the acute treatment of adults with mania associated with Bipolar Disorder. Two well-controlled trials demonstrated that Equetra was efficacious in the acute treatment of mania. Equetra treatment of manic subjects was reasonably safe and well tolerated. In my opinion, the treatment effect of Equetra was clinically significant. Furthermore, it seems reasonable to expect that one could generalize from the results of these trials to the general population of Bipolar Disorder patients experiencing an acute manic episode, since the study population represented well the general population of patients with Bipolar Disorder with acute mania.

Recommendation on Postmarketing Actions

7.2.13 Risk Management Activity

In long-term studies of Equetra in mania and Bipolar Disorder, the sponsor should monitor subjects closely for rash, hematologic abnormalities, increased cholesterol levels, liver function abnormalities, and weight gain. Clinicians should be aware of the potential of Equetra treatment to cause the abnormalities listed above.

7.2.14 Required Phase 4 Commitment

In a meeting with the sponsor on November 1, 2001, the Division requested that the sponsor conduct well-controlled, long-term efficacy trials in subjects with Bipolar Disorder, Manic or Mixed episode. The Division stated that a placebo-controlled relapse prevention design would be necessary. An open-label continuation study will not suffice. The long-term studies could be undertaken as a phase 4 commitment.

APPENDIX 10.1. DESCRIPTION OF EXTENSION STUDY 105.303

STUDY NUMBER	**105.303**
Study dates	January 9, 200 to January 28, 2002
Sites	22 sites in 12 states and D.C.
Primary Objectives	To provide prolonged treatment to subjects who had completed studies 301 or 302. To gather additional efficacy and safety data.
Subjects	92 subjects with Bipolar I Disorder, Manic or Mixed who completed study 301 or 302. Some of these subjects had been treated with Placebo during the acute trials. 44 subjects had been treated with Equetra, and 48 had been treated with Placebo
Design	Six-month open-label extension study of Equetra in subjects with Bipolar Disorder, Recently Manic who completed studies 105.301 or 105.302.

	Day 1 was the last day of double-blind treatment. During Days 2-19, double-blind treatment was gradually replaced by open-label treatment with Equetra. The maximum daily dose was 1600 mg/day. The primary efficacy variable was time to relapse
Disposition	Completed: 26% of subjects completed 6 months of treatment Discontinued: 74% of subjects discontinued before 6 months.
Efficacy results	Of the 77 ITT subjects, 11 (14.3%) relapsed during this 6-month open-label study (7 prior Equetra and 4 prior placebo). The mean of actual time to relapse for all 11 subjects who relapsed was 61.1 days (65.1 days for the 7 prior Equetra subjects who relapsed and 54.0 days for the 4 prior placebo subjects who relapsed).

Appendix 10.2.1. Disposition in Study 105.302 (Lithium Non-Responders)

DISPOSITION IN STUDY 105.302		
	Equetra	Placebo
No. of subjects randomized	29	30
No. ITT subjects	27 (93%)	30
No. of subjects completed	13 (45%)	19 (63%)
No. of subjects discontinued	16 (55%)	11 (37%)
Reasons for discontinuation		
Adverse event	6 (21%)	0
Subject Choice	5 (17%)	4 (13%)
Lack of efficacy	3 (10%)	7 (23%)
Lost to follow-up	1 (3%)	0
Protocol violation	1 (3%)	0

Appendix 10.2.1. Disposition in Extension Study 105.303

DISPOSITION IN EXTENSION STUDY 105.303			
	Subjects From Protocols 301 & 302		
	Equetra on Day 1	Placebo on Day 1	Total
Variable	N (%)	N (%)	N (%)
Enrolled	44 (100.0%)	48 (100.0%)	92 (100.0%)
Completed Study	11 (25.0%)	13 (27.1%)	24 (26.1%)
Discontinued Study	33 (75.0%)	35 (72.9%)	68 (73.9%)
Lost to Follow-up	7 (15.9%)	5 (10.4%)	12 (13.0%)
Adverse Event(s)	8 (18.2%)	11 (22.9%)	19 (20.7%)
Subject Choice	7 (15.9%)	8 (16.7%)	15 (16.3%)
Lack of Efficacy	6 (13.6%)	5 (10.4%)	11 (12.0%)
Protocol Violation	4 (9.1%)	5 (10.4%)	9 (9.8%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (2.3%)	1 (2.1%)	2 (2.2%)

Appendix 10.3. Baseline Demographics and Features of Illness in Pivotal Studies

	Study #105.301		Study #417.304		Combined Studies	
Treatment Group	SPD417	Placebo	SPD417	Placebo	SPD417	Placebo
No. in ITT Population	94	98	120	115	214	213
Country						
India	0 (0.0%)	0 (0.0%)	46 (38.3%)	45 (39.1%)	46 (21.5%)	45 (21.1%)
US	94 (100%)	98 (100%)	74 (61.7%)	70 (60.9%)	168 (78.5%)	168 (78.9%)
Age (yrs) - Mean (SD)	38.3 (10.7)	38.0 (11.3)	37.3 (11.1)	36.5 (10.9)	37.8 (10.9)	37.2 (11.1)
Age Category						
18-29	20 (21.3%)	23 (23.5%)	36 (30.0%)	32 (27.8%)	56 (26.2%)	55 (25.8%)
30-39	33 (35.1%)	31 (31.6%)	33 (27.5%)	39 (33.9%)	66 (30.8%)	70 (32.9%)
>=40	41 (43.6%)	44 (44.9%)	51 (42.5%)	44 (38.3%)	92 (43.0%)	88 (41.3%)
Gender						
Male	54 (57.4%)	46 (46.9%)	80 (66.7%)	85 (73.9%)	134 (62.6%)	131 (61.5%)
Female	40 (42.6%)	52 (53.1%)	40 (33.3%)	30 (26.1%)	80 (37.4%)	82 (38.5%)
Ethnic Origin						
White	70 (74.5%)	73 (74.5%)	53 (44.2%)	54 (47.0%)	123 (57.5%)	127 (59.6%)
Black	19 (20.2%)	16 (16.3%)	16 (13.3%)	12 (10.4%)	35 (16.4%)	28 (13.1%)
Hispanic	4 (4.3%)	7 (7.1%)	4 (3.3%)	0 (0.0%)	8 (3.7%)	7 (3.3%)
Asian/Pacific Islander	0 (0.0%)	2 (2.0%)	2 (1.7%)	2 (1.7%)	2 (0.9%)	4 (1.9%)
Native American	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	45 (37.5%)	47 (40.9%)	45 (21.0%)	47 (22.1%)
Weight (lbs)						
N	93	96	120	115	213	211
Mean (SD)	184.3 (50.5)	194.7 (52.3)	169.3 (51.8)	166.5 (50.6)	175.8 (51.7)	179.4 (53.1)
Current Bipolar Episode						
Manic	39 (41.5)	53 (54.1%)	95 (79.2%)	93 (80.9%)	134 (62.6%)	146 (68.5%)
Mixed	55 (58.5%)	45 (45.9%)	25 (20.8%)	22 (19.1%)	80 (37.4%)	67 (31.5%)
Years Since First Episode						
Mean (SD)	2.69 (2.69)	2.65 (1.72)	11.35 (9.85)	11.76 (9.49)	7.55 (8.72)	7.57 (8.40)

Appendix 10.4.1. Equetra Exposure in Person-Years

TABLE DURATION OF SUBJECTS RECEIVING STUDY MEDICATION ACCORDING TO DAILY DOSE AND DURATION OF THERAPY IN PHASE 3 STUDIES

	Equetra Daily Dose (mg/day)					
Drug Exposure (Years)	200	400-600	800-1000	1200-1400	1600	Total Carbatrol
Short Term Study (105.301)						
N	6	99	90	62	35	101
Sum (Person Years)	0.02	1.08	1.35	0.83	0.75	4.03
Short Term Study (105.302)						
N	1	27	25	21	8	28
Sum (Person Years)	0.00	0.30	0.38	0.23	0.15	1.06
Short Term Study (417.304)						
N	12	120	107	77	47	122
Sum (Person Years)	0.04	1.61	1.98	1.21	0.94	5.79
Long-term (#105.303)						
N	1	25	51	35	44	92
Sum (Person Years)	0.02	3.81	7.09	3.86	4.81	20.80
Short Term Studies						
N	19	246	222	160	90	251
Sum (Person Years)	0.07	2.98	3.71	2.27	1.84	10.89
Short and Long Term Studies						
N	20	259	248	184	124	299
Sum (Person Years)	0.09	6.79	10.80	6.13	6.65	31.69

Appendix 10.4.2. Equetra Exposure by Duration in the Pivotal Trials

	Study #105.301	**Study #417.304**	**Combined Studies**
Duration on Drug	N (%) of Patients	N (%) of Patients	N (%) of Patients

1-2 days	6 (6.4%)	4 (3.3%)	10 (4.7%)
3-4 days	2 (2.1%)	3 (2.5%)	5 (2.3%)
5-7 days	10 (10.6%)	8 (6.7%)	18 (8.4%)
8-14 days	24 (25.5%)	14 (11.7%)	38 (17.8)
15-21 days	35 (37.2%)	84 (70.0%)	119 (55.6%)
>21 days	17 (18.1%)	7 (5.8%)	24 (11.2%)
Total	94	120	214

Source: Table ISE.3.1

Appendix 10.4.3. Mean and Median Final Equetra Doses in the 3 Controlled Trials

Summary of Final Daily Equetra Dose Taken During Controlled Phase III Studies	
	Final Daily Carbatrol Dose (mg)
Combined Controlled Protocols (105.301, 105.302, 417.304)	
N	251
Mean (SD)	853.4 (435.82)
Min, Max	200, 1600
Median	800
Protocol 105.301	
N	101
Mean (SD)	952.5 (433.73)
Min, Max	200, 1600
Median	800
Protocol 105.302	
N	28
Mean (SD)	1050.0 (440.96)
Min, Max	200, 1600
Median	1100
Protocol 417.304	
N	122
Mean (SD)	726.2 (400.17)
Min, Max	200, 1600
Median	600

Appendix 10.5.1. Discontinuations Due to Adverse Events in the Pivotal Trials

Table . Discontinuations Due to Adverse Events- PIVOTAL

ADVERSE	EQUETRA	PLACEBO	RELATIONSHIP

EVENT	N= 223	N= 220	TO STUDY DRUG
Rash	3 (1.3%)	2 (1%)	Possible
Pruritus	3 (1.3%)	2 (1%)	Possible
Febrile illness	1 (0.4%)	0	Possible
Abnormal liver function tests	1 (0.4%)	0	Possible
Abdominal pain	0	1 (0.4%)	
Nausea	2 (1%)	1 (0.4%)	Possible
Vomiting	2 (1%)	1 (0.4%)	Possible
Diarrhea	0	2 (1%)	
Dizziness	3 (1.3%)	0	Probable
Exacerbation of mania	3 (1.3%)	3 (1.4%)	Unlikely
Nystagmus	1 (0.4%)	0	Probable
ST-t change and LBB block	1 (0.4%)	0	Possible
Asthma exacerbation	1 (0.4%)	1 (0.4%)	Unlikely
Hypertensive crisis	1 (0.4%)	0	Unlikely
Orbital fracture	0	1 (0.4%)	Not
Hallucination	1 (0.4%)	0	Unlikely
Depressed mood	1	1 (0.4%)	Unlikely
Asthenia	2 (1%)	0	Probable
Suicidal ideation	1 (0.4%)	1 (0.4%)	Unlikely
Anxiety	1 (0.4%)	0	Unlikely
Ataxia	2 (1%)	0	Probable
Somnolence	1 (0.4%)	0	Probable
Diplopia	1 (0.4%)	0	Probable

Appendix 10.5.2. Discontinuations Due to Adverse Events in Study 105.302 (Lithium Non-responders)

ADVERSE EVENT	TREATMENT	RELATIONSHIP TO EQUETRA
Erythematous rash, lymphadenopathy	Equetra	Probable
Dizziness, vomiting, diaphoresis	Equetra	Probable
Ataxia, light-headedness, nausea	Equetra	Probable
Generalized weakness	Equetra	Probable
Exacerbation of mania	Equetra	Unlikely
Agitation	Equetra	Unlikely

Appendix 10.5.3. Discontinuations Due to Adverse Events in Extension Study 105.303

	EQUETRA ON DAY 0	PLACEBO ON DAY 0
Body System/Preferred Term	(N=44)	(N=48)

	N (%)	N (%)
Number of subjects discontinued due to adverse events	8 (18%)	11 (23%)
Body as a Whole		
Abdominal Pain	0	1 (2%)
Suicide Attempt	0	1 (2%)
Digestive System		
Anorexia	0	1 (2%)
Diarrhea	1 (2%)	1 (2%)
Dyspepsia	1 (2%)	0
Liver Function Tests Abnormal	1 (2%)	1 (2%)
Nausea	0	1 (2%)
Tongue Edema	0	1 (2%)
Hemic/Lymphatic System		
Leukopenia	0	1 (2%)
Nervous System		
Agitation	1 (2%)	0
Anxiety	0	1 (2%)
Depression	1 (2%)	1 (2%)
Manic Depressive Reaction	3 (7%)	0
Manic Reaction	1 (2%)	1 (1%)
Somnolence	0	1 (2%)
Respiratory System		
Dyspnea	0	1 (2%)
Skin Appendages		
Rash	1 (2%)	3 (6%)

APPENDIX 10.6.1. Mean Serum Chemistry Changes in the 3 Controlled Trials

Table 18. Mean Changes from Baseline to Endpoint in Blood Chemistry Values for Parameters with Statistically Significant Differences in the SPD417 vs Placebo Groups in Short-Term Studies

Parameter	SPD417		Placebo		P-Value (a)
	Baseline	Change	Baseline	Change	
Albumin (g/dL)					
Mean	4.291	0.001	4.287	0.080	0.0020
SD	0.319	0.335	0.337	0.283	
Alkaline Phosphatase (IU/L)					
Mean	90.239	5.885	89.903	1.986	0.0081
SD	27.685	17.709	26.854	13.673	
Chloride (mEq/L)					
Mean	102.956	-0.584	103.218	0.282	0.0032
SD	3.095	4.358	3.269	3.398	
Cholesterol (mg/dL)					
Mean	187.052	21.504	191.749	0.772	<0.0001
SD	41.414	31.464	47.878	28.535	
Cholesterol: Direct HDL (mg/dL)					
Mean	44.153	3.676	41.956	0.500	0.0049
SD	12.428	10.234	11.876	7.638	
Cholesterol: LDL (mg/dL) (Friedwald Calculation)					
Mean	98.886	18.810	98.681	5.194	<0.0001
SD	32.669	24.231	38.220	26.830	
Total Bilirubin (mg/dL)					
Mean	0.366	-0.107	0.352	0.058	<0.0001
SD	0.234	0.236	0.219	0.251	
Total Calcium (mg/dL)					
Mean	9.363	-0.150	9.342	0.046	<0.0001
SD	0.434	0.503	0.422	0.554	
Total Protein (g/dL)					
Mean	7.445	0.041	7.473	0.143	0.0081
SD	0.586	0.588	0.611	0.535	
Uric Acid (mg/dL)					
Mean	4.991	-0.690	5.170	0.245	<0.0001
SD	1.324	0.957	1.463	0.978	

Appendix 10.6.2. Outliers in Analysis for Serum Chemistry Values (3 Controlled Trials)

Table 20. Most Frequently Occurring Shifts in Chemistry Parameters – Number and Percentage of Patients with Shifts from Normal to Abnormal

Parameter	Short-Term Studies		Long-Term Study
	SPD417 N (%)	Placebo N (%)	SPD417 N (%)
Normal to High			
Alkaline Phosphatase	19 (8.6%)	12 (5.4%)	8 (10.0%)
Cholesterol	44 (29.9%)	13 (10.7%)	9 (25.7%)
Cholesterol: Direct HDL	4 (5.6%)	0 (0.0%)	N/A
Cholesterol: LDL	19 (20.0%)	8 (9.2%)	N/A
Glucose	20 (9.9%)	14 (7.0%)	8 (9.9%)
SGOT	13 (5.5%)	10 (4.5%)	5 (6.0%)
SGPT	23 (10.8%)	9 (4.4%)	8 (10.5%)
Triglycerides	6 (6.6%)	11 (13.3%)	N/A
Normal to Low			
Cholesterol: Direct HDL	7 (9.7%)	10 (16.7%)	N/A
Glucose	10 (5.0%)	9 (4.5%)	0 (0.0%)
Total Bilirubin	27 (11.9%)	6 (2.6%)	4 (5.1%)
Uric acid	15 (6.4%)	4 (1.7%)	0 (0.0%)

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Appendix 10.6.3 Changes in Mean Hematology Parameters

Table 19. Mean Changes from Baseline to Endpoint in Hematology Values for Parameters with Statistically Significant Differences in the SPD417 vs Placebo Groups in Short-Term Studies

Parameter	SPD417		Placebo		P-Value (a)
	Baseline	Change	Baseline	Change	
Red Blood Cell Count (x 10^6/μL)					
Mean	4.676	-0.054	4.654	0.049	<0.0001
SD	0.455	0.268	0.582	0.288	
White Blood Cell Count (x 10^3/μL)					
Mean	7.878	-1.204	8.185	-0.183	<0.0001
SD	2.262	2.010	2.449	2.151	
Basophils (%)					
Mean	0.359	0.084	0.353	0.006	0.0040
SD	0.202	0.327	0.231	0.303	
Hematocrit (%)					
Mean	43.132	-0.512	43.177	0.263	0.0011
SD	4.171	2.643	4.472	2.796	
Hemoglobin (g/dL)					
Mean	14.260	-0.171	14.237	0.072	0.0015
SD	1.427	0.809	1.569	0.845	
MCH (pg)					
Mean	30.661	-0.036	30.858	-0.208	0.0341
SD	2.113	0.799	2.562	0.824	
MCV (μm^3) (FL)					
Mean	92.398	0.073	93.336	-0.436	0.0232
SD	5.844	2.075	7.260	1.941	
Reticulocytes (%)					
Mean	1.262	-0.152	1.266	0.013	0.0004
SD	0.629	0.516	0.658	0.531	

Appendix 10.6.3. Changes in Mean Hematology Values for the 3 Controlled Trials (Above)

Appendix 10.6.4. Outliers for Hematology Parameters in the 3 Controlled Trials

Table 21. Most Frequently Occurring Shifts in Hematology Parameters – Number and Percentage of Patients with Shifts from Normal to Abnormal

Parameter	Short-Term Studies		Long-Term Study
	SPD417 N (%)	Placebo N (%)	SPD417 N (%)
Normal to High			
MCV	6 (2.8%)	5 (2.7%)	10 (12.8%)
Monocytes	11 (5.1%)	9 (4.1%)	0 (0.0%)
Normal to Low			
RBC	5 (2.0%)	3 (1.3%)	6 (6.8%)
WBC	11 (4.6%)	4 (1.7%)	5 (5.7%)
Monocytes	10 (4.7%)	20 (9.2%)	2 (2.2%)
Reticulocytes	31 (14.6%)	10 (5.2%)	5 (6.6%)

Appendix 10.7, Changes in Mean Vital Signs and Weight

Table 22. Mean Changes in Vital Signs from Baseline to Endpoint

Parameter	SPD417 Short-Term Studies (Controlled Studies)		Placebo Short-Term Studies (Controlled Studies)		SPD417 Long-Term Study (Uncontrolled Study)	
	Baseline	Change	Baseline	Change	Baseline	Change
Systolic BP (mmHg)						
Mean	120.7	1.3	121.8	-0.3	120.6	-1.0
SD	14.36	13.25	13.37	13.07	14.44	13.45
Diastolic BP (mmHg)						
Mean	76.6	0.5	76.5	0.8	76.6	-0.4
SD	9.10	9.20	8.90	8.93	9.97	10.44
Pulse (bpm)						
Mean	78.5	0.6	78.5	-0.5	76.0	0.4
SD	10.60	13.16	10.17	11.47	9.62	10.79
Weight (lbs)						
Mean	177.6	2.2*	182.0	0.1	197.0	-0.9
SD	51.64	5.57	53.24	5.06	50.11	7.76

Appendix 10.8.1. Changes in Mean ECG Parameters

Table 23. Mean Changes in ECG Parameters from Baseline to Endpoint

Parameter	SPD417 Short-Term Studies (Controlled Studies)		Placebo Short-Term Studies (Controlled Studies)		SPD417 Long-Term Study (Uncontrolled Study)	
	Baseline	Change	Baseline	Change	Baseline	Change
Ventricular Rate (bpm)						
Mean	73.6	-1.1	73.0	-0.4	67.6	1.4
SD	14.96	15.11	13.58	13.11	11.60	12.12
PR (msec)						
Mean	160.4	5.6	162.2	1.9	167.8	0.5
SD	19.57	17.75	21.70	18.77	17.21	20.68
QRS (msec)						
Mean	94.4	0.8	95.8	-0.3	95.2	0.6
SD	8.08	8.37	9.43	8.90	8.51	10.33
QT (msec)						
Mean	369.9	-2.5	371.3	1.4	379.2	-1.6
SD	32.16	33.36	31.03	33.83	27.50	29.08
QTc (msec)						
Mean	404.8	-4.6	405.2	0.7	399.6	1.4
SD	27.74	29.51	25.17	25.48	28.70	28.71

Appendix 10.8.2 Outliers for ECG Parameters in all 4 Studies

List of Subjects with Normal Value at Baseline and Out-of-Range Value at Endpoint

Treatment GROUP	Patient No.	Visit	Ventricular Rate (BPM)	PR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	QTc (msec)
Equetra: short-term	105.301-001-013	Baseline	55	170	100	410	393
		Endpoint	77	201*	78	386	437
	105.301-004-007	Baseline	47	180	110	450	398
		Endpoint	55	200*	110	420	402
	105.301-028-012	Baseline	68	180	90	380	405
		Endpoint	69	200*	90	370	397
	105.302-034-204	Baseline	52	150	90	420	391
		Endpoint	33*	190	90	450	334
	417.304-006-002	Baseline	60	190	90	390	390
		Endpoint	63	220*	100	390	400
	417.304-023-001	Baseline	56	190	90	410	396
		Endpoint	84	230*	90	340	402
	417.304-051-021	Baseline	71	190	80	340	370
		Endpoint	63	230*	100	390	400
Placebo: short-term	105.301-019-005	Baseline	61	190	100	420	423
		Endpoint	68	240*	90	390	415
	105.301-029-005	Baseline	72	160	100	370	405
		Endpoint	81	200*	110	340	395
	105.301-030-010	Baseline	48	170	90	410	367
		Endpoint	45	200*	100	440	381
	417.304-012-006	Baseline	70	190	90	360	389
		Endpoint	71	200*	100	390	424
	417.304-018-009	Baseline	71	200	110	340	370
		Endpoint	77	190	120*	340	385
	417.304-024-007	Baseline	61	160	110	380	383
		Endpoint	62	170	120*	370	376
Equetra: long-term	105.303-005-002	Baseline	59	190	100	430	426
		Endpoint	46	200*	90	410	359
	105.303-005-007	Baseline	63	180	100	410	420
		Endpoint	65	200*	100	400	416
	105.303-030-013	Baseline	78	160	100	350	399
		Endpoint	66	200*	100	380	399
	105.303-030-204	Baseline	60	180	90	370	370
		Endpoint	50	210*	100	410	374
	105.303-035-202	Baseline	62	180	100	380	386
		Endpoint	81	170	120*	350	407

* Value meets defined outlier criteria.

Appendix 10.8.3. Outliers for Ventricular Rate in all 4 Studies

Ventricular Rate - Change from Baseline to Endpoint in Phase 3 Studies

		End-Study				
Treatment Group	Ventricular Rate (BPM) Baseline	NA	< 40	40 - < 120	>= 120	Total
Short-Term Studies: Equetra	Not Available (NA)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	2
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	31 (12.4%)	1 (0.4%)	217 (87.1%)	0 (0.0%)	249
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	32	1	218	0	251
Short-Term Studies: Placebo	NA	1 (33.3%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	3
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	36 (14.7%)	0 (0.0%)	209 (85.3%)	0 (0.0%)	245
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	37	0	211	0	248
Long-Term Study: Equetra	NA	2 (66.7%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	3
	< 40	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	40 - < 120	13 (14.6%)	0 (0.0%)	76 (85.4%)	0 (0.0%)	89
	>= 120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
	Total	15	0	77	0	92

Not Available (NA): Records are not available either at baseline or endpoint

Appendix 10.8.4. Changes in Mean PR Interval in all 4 Studies

PR Interval – Change from Baseline to Endpoint in Phase 3 Studies

		End-Study			
Treatment Group	PR Interval (msec) Baseline	NA	< 200	>= 200	Total
Short-Term Studies: Equetra	Not Available (NA)	3 (75.0%)	1 (25.0%)	0 (0.0%)	4
	< 200	30 (12.7%)	200 (84.7%)	6 (2.5%)	236
	>= 200	1 (9.1%)	5 (45.5%)	5 (45.5%)	11
	Total	34	206	11	251
Short-Term Studies: Placebo	NA	1 (25.0%)	3 (75.0%)	0 (0.0%)	4
	< 200	35 (15.2%)	192 (83.1%)	4 (1.7%)	231
	>= 200	1 (7.7%)	6 (46.2%)	6 (46.2%)	13
	Total	37	201	10	248
Long-Term Study: Equetra	NA	2 (66.7%)	1 (33.3%)	0 (0.0%)	3
	< 200	13 (15.1%)	69 (80.2%)	4 (4.7%)	86
	>= 200	0 (0.0%)	2 (66.7%)	1 (33.3%)	3
	Total	15	72	5	92

Not Available (NA): Records are not available either at baseline or endpoint

Appendix 10.8.5. Outliers for QRS Interval in all 4 Studies

QRS Interval – Change from Baseline to Endpoint in Phase 3 Studies

		End-Study			
Treatment Group	QRS Interval (msec) Baseline	NA	< 120	>= 120	Total
Short-Term Studies: Equetra	Not Available (NA)	1 (50.0%)	1 (50.0%)	0 (0.0%)	2
	< 120	30 (12.1%)	217 (87.9%)	0 (0.0%)	247
	>= 120	1 (50.0%)	0 (0.0%)	1 (50.0%)	2
	Total	32	218	1	251
Short-Term Studies: Placebo	NA	1 (33.3%)	2 (66.7%)	0 (0.0%)	3
	< 120	36 (14.9%)	204 (84.3%)	2 (0.8%)	242
	>= 120	0 (0.0%)	0 (0.0%)	3 (100%)	3
	Total	37	206	5	248
Long-Term Study: Equetra	NA	2 (66.7%)	1 (33.3%)	0 (0.0%)	3
	< 120	12 (13.8%)	74 (85.1%)	1 (1.1%)	87
	>= 120	1 (50.0%)	0 (0.0%)	1 (50.0%)	2
	Total	15	75	2	92

Not Available (NA): Records are not available either at baseline or endpoint

Robert Levin, M.D., November 22, 2004
Medical Reviewer,
FDA, CDER, ODE1, DNDP, HFD-120

Cc: NDA
T Laughren
P Andreason
D Bates

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

/s/

Robert Levin
11/29/04 10:15:14 AM
MEDICAL OFFICER

Thomas Laughren
11/29/04 01:45:10 PM
MEDICAL OFFICER
I agree that this NDA is approvable; see memo to file for more detailed comments--TPL