2.0 Synopsis

<table>
<tr><td>Name of Company:
Abbott Laboratories
Name of Finished Product:
Depakote, Depakote ER
Name of Active Ingredient:
Divalproex sodium</td><td>Individual Study Table Referring to Item of the Submission:

Volume:
Page:</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="3">Title of Study:
A Randomized, Double-Blind Study of Depakote Monotherapy, Olanzapine Monotherapy, and Combination Therapy of Depakote Plus Olanzapine in Stable Subjects during the Maintenance Phase of Bipolar Illness</td></tr>
<tr><td colspan="3">Investigator(s): Multicenter Trial (Investigator information on file at Abbott Laboratories)</td></tr>
<tr><td colspan="3">Study Site(s): Multicenter Trial (Investigator information on file at Abbott Laboratories)</td></tr>
<tr><td colspan="3">Reason for Abbreviated Report:
In accordance with the FDA guidance on abbreviated reports, this study summary is submitted as an abbreviated clinical study report due to the sponsor's decision to prematurely discontinue the study.</td></tr>
<tr><td colspan="3">Publication: N/A</td></tr>
<tr><td colspan="2">Study Period (Years):
Study Initiation Date: September 3, 2003
(first screening procedure)
Date First Subject Dosed: September 16, 2003
Date Last Subject Completed Dosing: July 6, 2004
(study was prematurely discontinued)
Date of Last Study Procedure: July 23, 2004</td><td>Phase of Development: 4</td></tr>
<tr><td colspan="3">Objective:
The objective of this study was to assess efficacy and safety of continued combination therapy using Depakote plus olanzapine, vs. Depakote monotherapy and olanzapine monotherapy in stable subjects during the maintenance phase of bipolar illness.</td></tr>
<tr><td colspan="3">Methodology:
This was a Phase 4, randomized, double-blind, placebo-controlled, multicenter 20-week study comparing Depakote monotherapy and olanzapine monotherapy to combination therapy of Depakote and olanzapine in subjects with stable bipolar illness during the maintenance phase of treatment. Approximately 180 subjects (60 per treatment arm) were to be randomized at approximately 20 sites.</td></tr>
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Subjects eligible to enter the study were to be clinically stable for at least six weeks on combination therapy of Depakote plus olanzapine for bipolar illness. Clinical stability was defined as a preceding period of at least six consecutive weeks with no more than minimal symptoms of bipolar illness, no psychiatric hospitalizations, and no increase in the intensity of clinical interventions, based on the investigator's assessment. Additionally, a CGI-S score of ≤ 3, an MRS score of ≤ 12, and a DSS score of ≤ 13 on two consecutive ratings separated by at least five days (during Screening and again at Day 1) were required for randomization. Subjects were also required to identify a most bothersome side effect attributed to combination therapy (Depakote plus olanzapine), which made switching to monotherapy desirable. Subjects who entered the study on Depakote continued taking Depakote or matching placebo after randomization and subjects who entered the study on Depakote ER continued to take Depakote ER or matching placebo after randomization. Subjects continued on the same dosing schedule (time of administration and frequency) for both Depakote and olanzapine after randomization as they had before randomization. Subjects were stratified according to the formulation they were taking at the time of Screening.

Subjects underwent Screening procedures, including a medical and psychiatric history, the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR), Mania Rating Scale (MRS) and Depressive Syndrome Scale (DSS) derived from the Schedule for Affective Disorders and Schizophrenia-Change version (SADS-C), the Clinical Global Impression Severity Scale (CGI-S), the UKU side effect rating scale, urine drug screen, urine pregnancy test (for female subjects), and clinical laboratory tests (including serum valproate and olanzapine levels). Screening was to be at least five days in length, but no more than 14 days.

At the Day 1 visit, the SADS-C (which includes the MRS and the DSS), the CGI-S, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), a movement rating scale battery (SAS, BAS, and AIMS), the UKU side effect rating scale, a physical examination (including vitals signs and weight), and a 12-lead electrocardiogram were performed. Subjects who met clinical stability criteria on Day 1 were randomized and entered into the 8-week double-blind taper period.

Subjects who met all inclusion and exclusion criteria were randomized to one of three treatment arms at Day 1: Depakote monotherapy, olanzapine monotherapy, or continued combination therapy with Depakote plus olanzapine. At least five days prior to randomization, subjects with a Depakote dose that was not a multiple of 500 mg were to have their dose increased to the nearest multiple of 500 mg, and subjects with an olanzapine dose that was not a multiple of 5 mg were to have their dose increased to the nearest multiple of 5 mg. Subjects randomized to the Depakote monotherapy arm were blindly tapered completely off olanzapine according to a decreasing dose schedule over the first 8-weeks of the treatment period and then maintained only on Depakote at their original Day 1 dose through the remainder of the 12-week double-blind maintenance period. Subjects randomized to the olanzapine monotherapy arm were blindly tapered completely off Depakote according to a decreasing dose schedule over the first 8-weeks of the treatment period and then be maintained only on their Day 1 dose of olanzapine through the remainder of the double-blind maintenance period. Subjects randomized to the combination therapy arm were maintained on their respective Day 1 Depakote and olanzapine doses throughout the 20-week treatment period.

During the course of the study, batteries of psychiatric and movement rating scales, and quality of life and pharmacoeconomic data were collected. Safety was monitored by the UKU side effect rating scale, measurements of vital signs and body weight, physical examinations, routine clinical laboratory tests, ECGs, and the assessment of spontaneously reported adverse events.

Number of Subjects (Planned and Analyzed):
Planned: 180 Randomized: 36 Treated: 35 Completed: 10 Evaluated for Safety: 35

Diagnosis and Main Criteria

Inclusion Criteria:

- Subject was between 18 and 65 years of age at the time of randomization.
- Subject had a DSM-IV-TR primary diagnosis of Bipolar I Disorder as confirmed by the SCID at Screening.
- Subject was to be an outpatient receiving treatment with a combination of Depakote plus olanzapine for their bipolar illness and was to have been considered clinically stable (*e.g.*, no more than minimal symptoms, no psychiatric hospitalizations, no increase in intensity of clinical interventions) for the preceding 6 consecutive weeks, prior to Screening, based on the Investigator's assessment.
- Subject identified at Screening the most bothersome side effect listed on the UKU, which made switching to monotherapy desirable.
- Subject had an MRS total score of ≤ 12 on two consecutive ratings, separated by at least five days (Screening and Day 1).
- Subject had a DSS score of ≤ 13 on two consecutive ratings, separated by at least five days (Screening and Day 1).
- Subject had a CGI-S score ≤ 3 on two consecutive ratings, separated by at least five days (Screening and Day 1).
- Subject had a trough serum valproate level ≥ 45 mcg/mL and a maximum allowable dose of Depakote of 3000 mg/day at Screening. If a subject was taking a dose of Depakote that was < 1000 mg/day, the Investigator reviewed the case with the Sponsor prior to enrollment.
- Subject had an olanzapine dose between 5 mg/day and 20 mg/day at Screening.
- Subject's doses of olanzapine and Depakote were not to have been adjusted (increased or decreased) within the 30 days prior to Screening, with the exception of necessary rounding (as specified in Section 5.5.1.1 in the protocol).

Exclusion Criteria:

- Subject's first manic episode occurred after the age of 60.
- Subject had taken antipsychotics, mood stabilizers, or non-benzodiazepine anticonvulsant medications (unless specifically for seizure control) other than Depakote or olanzapine in the six weeks prior to randomization.
- Subject had a known history of non-response to either Depakote or olanzapine monotherapy for the treatment of bipolar disorder, per Investigator assessment, as evidenced by medical record documentation, or an observed, prospective history reported by the Investigator.
- Subject was pregnant or intended to become pregnant during the study.
- Subject had been admitted to the hospital in the past six weeks for psychiatric treatment.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:		
	Depakote	**Placebo for Depakote**
Dosage Form	Tablet	Tablet
Strength (mg)	500 mg	N/A
Mode of Administration	Oral	Oral
NPRO Number	ER: 0753, 0861, 1102, 1145, 1152 DR: 0965	ER: 0753, 0861, 1102, 1145, 1152 DR: 0965
Bulk Product Lot Number	[redacted]	[redacted]
N/A - not applicable		

Duration of Treatment:

This 20-week double-blind study consisted of two parts: an 8-week taper period, and a 12-week maintenance period.

Reference Therapy, Dose and Mode of Administration, Lot Number:		
	Olanzapine	**Placebo for Olanzapine**
Dosage Form	Encapsulated tablet	Encapsulated tablet
Strength (mg)	5 mg (2 x 2.5 mg tablets per capsule)	N/A
Mode of Administration	Oral	Oral
NPRO Number	0753, 0861, 1102, 1145, 1152, 0956	0753, 0861, 1102, 1145, 1152, 0956
Bulk Product Lot Number	[redacted]	[redacted]
N/A - not applicable		

Criteria for Evaluation

Safety:

Safety was evaluated through the UKU side effect rating scale, measurements of vital signs and body weight, physical examinations, routine clinical laboratory tests, ECGs, and assessment of spontaneously reported adverse events.

Efficacy:

The psychiatric rating scales included the following: CGI-S (used to assess the subject's current clinical symptoms); the CGI-I (used to assess change in the subject's clinical symptoms since Day 1); MRS and DSS (derived from the SADS-C), were used to evaluate a subject's behavior during the previous week.

Movement Rating Scales:

The movement rating scales included the following: SAS, BAS, and AIMS. All movement scales were to be scored as the subject appeared at the time of the evaluation and not relative to any other time.

Statistical Methods:

Safety:

All subjects who received at least 1 dose of study drug were evaluated for safety. The primary treatment group comparisons were Depakote and olanzapine combination therapy *vs.* Depakote and olanzapine alone. The two monotherapy treatment groups were also compared using the following: UKU side effect rating scale, adverse events, clinical laboratory determinations, and vital sign values meeting Abbott-defined criteria for potential clinical significance were identified.

Efficacy:

Efficacy data were not analyzed for this abbreviated report.

Summary of Results:

Safety Results:

The overall mean duration of study drug exposure was 93 days in the Depakote group, 57 days in the olanzapine group, and 89 days in the combination group. Among Depakote-treated subjects, the mean daily Depakote dose during the maintenance period was 1150 mg for the Depakote group and 1214 mg for the Combination group. For olanzapine subjects, the mean daily olanzapine dose during the maintenance period was 11.7 mg for the Olanzapine group 11.4 mg for the Combination group.

The incidence of adverse events was similar across treatment groups. The most commonly experienced adverse events (more than two subjects) in the Depakote group were asthenia, diarrhea, nausea, headache, depression, nervousness, insomnia, and somnolence. Among subjects in the olanzapine group, depression, sleep disorder and somnolence were the most commonly reported adverse events. Sleep disorder, tremor, abnormal dreams, and sweating were the most commonly reported adverse events in the combination group.

One subject in the olanzapine group had a serious adverse event of psychosis which led to premature discontinuation. Three additional subjects had adverse events leading to premature discontinuation – two in the olanzapine group and one in the combination group. There were no deaths during this study.

There were few subjects who developed potentially clinically significant laboratory abnormalities, however, these were not clinically meaningful. There were no serious adverse events associated with abnormal laboratory values reported during this study.

There were no potentially clinically significant vital sign values and mean changes from baseline to final values in vital signs were comparable between treatment groups. There were no statistically significant differences between treatment groups for mean change from baseline to final value for weight or BMI. One subject in the Depakote group and three subjects in the combination group had at least a 7% weight gain from baseline to final value. Overall, there was no evidence of treatment group differences in the change in most bothersome side effect as assessed by the UKU.

Conclusions:

This study was designed to compare Depakote monotherapy and olanzapine monotherapy to combination therapy of Depakote and olanzapine in adult subjects with stable bipolar illness during the maintenance phase of treatment. Thirty-five subjects had enrolled and received study drug when the sponsor discontinued the study due to slow enrollment.

In this limited sample of subjects with bipolar disorder who had been taking a combination of Depakote and olanzapine for at least six weeks prior to randomization, Depakote and olanzapine were generally well tolerated. There were no clinically meaningful trends in vital signs, clinical laboratories, or body weight. Overall, there were no clinically significant safety concerns identified in this study.