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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NA
Generic drug name:	Sodium Valproate Chronosphere®	**Study Code:**	EFC_5196
		Date:	03/Aug/2007

Title of Study: A twelve-week, open, randomised trial comparing Sodium Valproate Chronosphere® to Lithium in Bipolar I patients suffering from a manic episode.

Investigators: This was a multicentre study, involving investigators across 36 active centres, in 13 countries.

Study centres: A total of 36 active centres recruited 347 patients in this study.

Publication (reference): None

Studies period (months): 15 Date of first enrolment: 16-Apr-04 Date of last patient completed: 02-Jun-05	**Phase of development:** III

Objectives:

Primary objective:

- To compare the efficacy of valproate to lithium in Bipolar I patients suffering from a hypomanic or manic episode according to the Diagnostic and Statistical Manual of Mental Disorder – Fourth Edition – Text revision (DSM IV TR (APA 2000)) after 3 weeks (D21) and 12 weeks (D84) of treatment.

Secondary objectives:

- To evaluate the clinical and biological safety of valproate compared to lithium.
- To assess patient status 3 weeks (D21) and 12 weeks (D84) after inclusion
- To evaluate patient satisfaction

Methodology: This was an international, Phase III, open study comparing 2 parallel groups of patients allocated to a flexible dose of either valproate or lithium (1:1), for 12 weeks. The study consisted of 2 phases:

- Phase A: a 3-day wash-out period (which could be reduced to 1 day in the event of aggravated symptomatology);
- Phase B: a 12-week, open, treatment period, during which eligible patients were treated with an initial dose of either 20 mg/kg/day valproate or 400 mg/day lithium carbonate.

From Day 4, the dose of either valproate or lithium was adjusted according to clinical judgment and plasma concentration.

Visits were scheduled on Day -3 (D-3), Day 0 (D0), Day 4 (D4), Day 7 (D7) (optional), Day 10 (D10), Day 14 (D14) (optional), Day 21 (D21), Day 42 (D42), Day 63 (D63), and Day 84 (D84).

Number of patients:

- Planned: 300
- Randomised: 300
- Safety population: 299
- Intent-to-treat (ITT) population: 298
- Per protocol (PP) population: 293

Diagnosis and main criteria for inclusion:

Male and female patients aged 18 to 75 years (inclusive) with a current diagnosis of Bipolar I disorder (according to the DSM IV TR), who were suffering from a manic episode and who had had at least 1 hypomanic/manic or 1 major depressive episode within the 5 years preceding the current episode.

Test product, dose, and mode of administration:

Sodium valproate: sachets containing 250 mg and 500 mg of Depakine Chronosphere®

Mode of administration: oral route (in cold, soft food, or in cold liquid)

Dose:

- From Day 0 to Day 3: 20 mg/kg/day of sodium valproate;
- From Day 4: the dosage was adjusted according to clinical judgment and plasma concentration of valproate. This concentration should have ranged between 50 µg/mL to 150 µg/mL. The dose of valproate was to be adapted in steps of 250 or 500 mg/day.

Reference therapy dose, and mode of administration:

Lithium carbonate: breakable tablets containing 400 mg of Priadel®

Mode of administration: oral route

Dose:

- From Day 0 to Day 3: 400 mg/day lithium;

- From Day 4: the dosage was adjusted according to clinical judgment and plasma concentration of lithium. This concentration should have ranged between 0.8 mmol/L to 1.2 mmol/L. The dose of lithium was to be adapted in steps of 200 mg/day or 400 mg/day.

Duration of treatment: 12 weeks

Criteria for evaluation:

Primary efficacy criteria:

The percentage of patients in remission, defined as a Young Mania Rating Scale (YMRS) score = 12 at Day 84 last observation carried forward (D84 LOCF, or DEnd) and a reduction of at least 2 points on the Clinical Global Impressions Scale for use in Bipolar Illness (CGI-BP) severity of mania.

Secondary efficacy criteria:

- Changes in YMRS scores between D0 and DEnd;
- Percentage of responders at DEnd, defined as a decrease of at least 50% in the YMRS between D0 and DEnd;
- Percentage of responders at Day 21 LOCF (D21 LOCF, or DEnd21), defined as a decrease of at least 50% in the YMRS between D0 and DEnd21;
- Sustained response, defined as a 50% reduction in the YMRS score and a Montgomery and Asberg Depression Rating Scale (MADRS) score = 14, which lasted for at least 2 consecutive, scheduled visits;
- Change in CGI-BP between D0 and DEnd;
- Change in the Global Assessment Scale (GAS) between D0 and DEnd;
- Change in the MADRS between D0 and DEnd;
- Percentage of relapses, defined as having sustained response and an increase of at least 25% of the YMRS total score (with a minimum YMRS total >12) or MADRS total score >14;
- Patient satisfaction (patient CGI-BP) at DEnd.

Safety criteria:

- The incidence of treatment-emergent adverse events (TEAEs);
- Vital signs parameters (including systolic and diastolic blood pressure, heart rate, and weight);
- 12-lead electrocardiogram (ECG);
- Laboratory data (including haematology, biochemistry, urinalysis, and thyroid function tests);
- Plasma concentration of valproate and lithium at D4 and D84 or premature withdrawal (D84/PW).

Statistical methods:

The difference between treatment groups in the percentage of patients in remission was calculated (plus the 95% confidence interval (CI)). Valproate was considered non-inferior to lithium if the absolute value of the lower limit of the 1-sided 97.5% CI for the treatment difference was > -15%. In addition, a logistic regression analysis was conducted on the primary outcome measure (including terms for treatment and country). The use of baseline YMRS score as a covariate was to be investigated. The odds-ratio for valproate/lithium and its associated 95% CI were presented. Missing data were handled using the last observation carried forward (LOCF) approach and the mixed model for repeated measurements (MMRM) approach[#].

Adverse events were presented using descriptive statistics.

No formal statistical analysis for the plasma drug concentration was planned for this study.

Results:

Three hundred patients were randomised, with 149 patients receiving valproate and 151 patients receiving lithium. A total of 109 patients (73.2%) in the valproate group and 113 patients (74.8%) in the lithium group completed the study (a total of 222 patients, 74.0%).

Primary Efficacy Variable

The results from this study show that valproate met the criterion for non-inferiority to lithium.This was the case regardless of whether the LOCF or MMRM approach was used, and regardless of whether the PP or ITT population was used. Using the LOCF approach in the PP population, remission was recorded for 72.3% of patients in the valproate group and 65.5% of patients in the lithium group, with a difference of 6.78 (95% CI: -3.80, 17.36). The odds ratio was 1.616 (95% CI: 0.940, 2.779).

Secondary Efficacy Variables

Analysis of the secondary variables (change in YMRS, percentage of responders at DEnd, percentage of responders at DEnd21, percentage of patients with sustained response, change in CGI-BP, change in GAS, change in MADRS, relapses, and patient satisfaction) indicated that valproate was similar (and not worse) than lithium, and there were no statistically significant differences between the 2 treatments.

Safety

The percentage of patients who experienced at least 1 TEAE was similar in both groups (44.3% in the valproate group and 44.0% in the lithium group). The TEAEs reported by patients in the 2 treatment groups

were unremarkable of those commonly documented to occur in response to valproate and lithium treatment. The most frequently reported TEAEs (> 5.0%) in any treatment group were tremor (1.3% in the valproate group versus 16.7% in the lithium group); nausea (11.4% in the valproate group versus 9.3% in the lithium group); weight gain (9.4% in the valproate group versus 4.0% in the lithium group); diarrhoea (7.4% in the valproate group versus 4.0% in the lithium group) and fatigue (6.0% in the valproate group versus 1.3% in the lithium group). The majority of treatment-related TEAEs were of mild or moderate intensity and most recovered during the study, with few requiring treatment.The majority of weight gain cases were treatment-related, and just less than half of these patients recovered. Treatment consisting of diet advice was given to 2 patients. All cases of tremor were treatment-related, and most of the patients recovered and did not need treatment.

No deaths or suicide attempts were reported in this study.There were 3 serious TEAEs (in 3 patients) during the study, all of which occurred in the lithium group. These events consisted of vomiting, polydipsia, and mania, and were all considered treatment-related by the investigator*. All 3 events led to discontinuation of the study drug, and treatment was required for the events of vomiting and mania. All 3 patients recovered from the events.

Withdrawal due to TEAEs occurred more frequently in the lithium group (9.3%) than in the valproate group (3.4%). The most frequently reported TEAEs (> 1% in any treatment group) leading to withdrawal from the study were diarrhoea, nausea, tremor, and depression (all reported by 1.3% of the patients in the lithium group versus 0.0%, 07%, 0.0%, and 0.7%, respectively, in the valproate group)

None of the PCSAs in laboratory parameters was considered clinically significant and there were no notable vital signs abnormalities reported. However, it should be noted that the number of patients experiencing a potentially clinically significant abnormalty (PCSA) of weight increase (ie, an increase of 7% or more from baseline) was higher in the valproate group (12.8%) compared to the lithium group (6.7%).

Date of report: 06-Jun-06

* SAE of Polydipsia (patient TR0201) was related to the study drug by the investigator as per AE form (October 4th 2004) and therefore in the clinical database. However, as per a letter signed by the investigator and received by sanofi-aventis pharmacovigilance department on July 5th 2005,"*the AE is not related with the investigation drugs*". Therefore the investigator's relationship to the study drug was updated from "yes" to "no" in sanofi-aventis pharmacovigilance database.