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<b>Sponsor/company:</b>	Bristol-Myers Squibb and Sanofi-Aventis	<b>ClinialTrials.gov Identifier:</b>	NCT00264173
<b>Generic drug name:</b>	Sodium Valproate	<b>Study Code:</b>	R_8740
		<b>Date:</b>	15 Nov 2007

**Title of Study:** A twelve-week, open, randomized trial comparing valproate to lithium in Bipolar I patients suffering from a manic episode

– **Investigators:**

Bulgaria: 3 centres:

- Assoc. Pr. L. Hranov, University Hospital "St. Naum" - Sofia
- Dr. Todor Tolev, State Psychiatric Hospital "Dr. G. Kissiov" - Radnevo
- Dr. Loris Sayan, District Dispansery for Psychiatric Disorders "Prof. Iv. Temkov" – Burgas

Taiwan: 4 centres

- Dr. Ying-Chiao Lee, Veterans General Hospital Taipei, Taiwan
- Dr. Shin-Min Lee, Dr. Ding-Lieh Liao, Dr. Wan-Hsiang Tai, Dr. Chian-Jue Kuo, Bali Psychiatric Center, Taipei, Taiwan
- Dr. Tzung-Jeng Hwang, Dr. Hsin-Nan Lin, National Taiwan University Hospital, Taipei, Taiwan
- Dr. Shing-Yaw Wang, Dr. Ching-Hua Lin, Kai-Suan Psychiatric Hospital, Taipei, Taiwan

Hong Kong: 1 centre

- Dr. Eric Chen, Queen Mary Hospital, Kwai Chung Hospital and Pamela Youde Nethersole Eastern Hospital, Hong Kong

Malaysia: 3 centres

- Prof. Hussain Habil, University Malaya Medical Centre, Department of Psychiatry, Lembah Pantai, 59100 Kuala Lumpur, Malaysia
- Dr. Jaya Prakash Reddy, Universiti Kebangsaan Malaysia, Psychiatry, Jalan Yacob Latiff, Bandar Tun Razak, 56000 Cheras, Malaysia
- Dr. Suarn Singh, Hospital Kota Bharu, Department of Psychiatry, Jalan Hospital, 15000 Kota Bharu, Kelantan, Malaysia

Russia: 6 centres

- Sergei Mosolov, Psychiatric Research Institute, Poteshnaya st., 3, 107076 Moscow
- Yuri Aleksandrovsky, Alla Avedisova, V.P.Serbsky social and forensic psychiatry research centre, Kropotkinsky pereulok, 23, 123367 Moscow
- Galina Panteleeva, Mental Health Research Centre of Russia Medical Sciences Academy, Kashirskoye shosse, 3, 115522 Moscow
- Mikhail Ivanov, The St.Petersburg V.M.Bekhterev Psychoneurological Research Institute, Bekhtereva st., 3, 192019 St.-Petersburg
- Nikolai Neznanov, Saint-Petersburg Academy of Medicine (Psychiatry Department), Tolstova st., 6/8, 197089 St.-Petersburg
- Evgenia Rebrova, City psychiatric hospital N 3 named after I.I.Skvortsova-Stepanova, Fermskoye shosse, 36, 197341 St.-Petersburg

Thailand: 4 centres

- Lt.Col.Thawatchai Leelahana, Dept of psychiatry and Neurology, Phramongkutklo Hospital - Bangkok
- Assist.Prof.Suttiporn Janenawasin, Dept of psychiatry, Faculty of Medicine, Siriraj Hospital - Bangkok
- Dr Nipat Karnjanathanalears, Dept of psychiatry, Faculty of Medicine, Chulalongkorn Hospital - Bangkok
- Assoc.Prof. Ronnachai Kongsakon, MD, Dept of psychiatry, Faculty of Medicine, Ramathibodi Hospital - Bangkok

A Steering Committee followed the study.

Steering Committee chairman:

Pr Charles Bowden, University of Texas (USA)

Steering Committee members:

Dr. Luchezar Hranov (Bulgaria)

Dr. Eric Chen (Hong Kong)

Pr. Hussain Habil (Malaysia)

Pr. Sergei Mosolov (Russia)

Dr. Li Shu Chuen (Singapore)

Dr. Hsin-Nan Lin (Taiwan)

Dr. Ronnachai Kongsakon (Thailand)

**Study centre(s):** 21 centres: Bulgaria: 3 centres, Taiwan: 4 centres, Hong Kong: 1 centre, Malaysia: 3 centres, Russia: 6 centres, Thailand: 4 centres

**Publication (reference):** NA

**Studied period (years):**

28/01/2004 (date of first enrolment)

12/02/2006 (date of last completed)

**Phase of development:** Phase IV

**Objectives:**

The primary objective was to compare the efficacy of valproate to lithium in Bipolar I patients suffering from a manic or a mixed episode according to DSM IV TR (APA 2000) over a period of 12 weeks of treatment

The secondary objectives were to evaluate the clinical and biological safety of valproate compared to lithium and to assess the cost-effectiveness of valproate compared to lithium in the management of bipolar patients

**Methodology:**

International, randomized, open study, comparing two parallel groups of patients allocated to a flexible dose of either valproate or lithium over a period of 12 weeks

**Number of patients (planned and analysed):**

Planned: 270 randomized patients (135 patients in each group).

Randomized and Treated: 270 patients were randomized, 130 in the valproate group and 138 in the lithium group. Two patients were randomized but not treated.

Evaluated :

Efficacy: 257 patients in the ITT population, 122 in the valproate group and 135 in the lithium group ; 254 patients in the per protocol population, 122 in the valproate group and 132 in the lithium group

Safety: 268 patients, 130 in the valproate group and 138 in the lithium group

**Diagnosis and main criteria for inclusion:**

In- or out-patients of either sex, aged 18-75, having given their written informed consent and able to comply with the protocol, with a current diagnosis of Bipolar I Disorder according to DSM IV TR, suffering from a current manic episode or a mixed episode according to DSM IV TR, with a history of at least one manic episode within the previous 3 years, with a minimum total score on the Young Mania Rating Scale of 18 at Screening and Baseline

**Test product, dose and mode of administration:**

Valproate: tablets of Depakine / Epilim Chrono®

Dose (oral route)

- from D0 to D5: the nearest dose to 20 mg/kg/day of Depakine / Epilim Chrono®
- from D5: the dosage was to be adjusted according to clinical judgment and serum concentration of valproic acid. This concentration should range between 70 to 125 µg/ml.

In case of important side effects, a decrease of valproate was allowed to 15 mg/kg/day

In case of non response, the investigator was allowed to switch the patient to the other treatment arm. This treatment switch could only be performed after D21

**Duration of treatment:**

12 weeks (84 days)

**Reference therapy, dose and mode of administration:**

Lithium carbonate: available forms in each country, preferably a sustained release form

Dose (oral route) :

- from D0 to D5: the nearest dose to 800 mg/day (between 600 and 900 mg/day)
- from D5: the dosage was to be adjusted according to clinical judgment and serum concentration of lithium. This concentration should range between 0.8 to 1.2 mmol/l.

In case of important side effects, a decrease was allowed to meet lithium serum concentration from 0.6 to 0.8 mmol/l

In case of non response, the investigator was allowed to switch the patient to the other treatment arm. This treatment switch could only be performed after D21

**Criteria for evaluation:**

**Efficacy:**

Young Mania Rating Scale (YMRS) score, Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP), Montgomery and Asberg Depression Rating Scale (MADRS) score

**Safety:**

Adverse events reported by the patient or noted by the investigator, physical examination, standard hematology and blood chemistry, standard electrocardiogram  
Plasma concentrations were to be assessed at D5 and at D84 or premature withdrawal. Other assays were to be done according to clinical judgment and/or practice

**Statistical methods:**

The primary criterion was defined as the change from baseline to the end of study in the YMRS. The primary analysis was a fixed model analysis of variance (ANOVA) with treatment and country as main factors. The primary efficacy analysis was to be performed on both ITT and PP populations

**Summary:**

Most patients were female (54% in the valproate group and 63% in the lithium group) and mean age was  $38.5 \pm 12.6$ . Last episode was a manic episode for 68.3% of valproate patients and for 62.5% of lithium patients, and a major depressive episode for 16.7% of valproate patients and for 19.5% of lithium patients, and this episode occurred  $1.5 \pm 1.5$  years ago for valproate patients and  $1.3 \pm 1.2$  years ago for lithium patients. The mean number of previous episode was  $5.7 \pm 5.7$  for valproate patients and  $5.8 \pm 5.6$  for lithium patients. At baseline, the delay since diagnosis of bipolar disorder was  $6.9 \pm 6.5$  years for patients randomized in the valproate group vs  $7.4 \pm 8.8$  in the lithium group. At baseline, YMRS score was  $24.1 \pm 5.3$  in valproate patients and  $24.4 \pm 5.0$  in lithium patients, and MADRS score was  $4.9 \pm 3.9$  in valproate patients and  $5.5 \pm 4.8$  in lithium patients.

**Efficacy Results:**

- At study end, in the ITT population, the mean decrease from baseline for YMRS was  $17.3 \pm 9.4$  for patients treated with valproate and  $15.8 \pm 5.3$  for patients treated with lithium. Both the inferior and superior limits of the 90% confidence interval of the difference on change in YMRS between baseline and end of the study  $[-0.69 ; 3.31]$  are inside the equivalence limits predefined in protocol  $[-4 ; +4]$ . Therefore, the clinical equivalence of valproate compared to lithium is demonstrated (Primary Efficacy Analysis). Similar results were obtained on the Per Protocol population.
- Changes from baseline in YMRS score: no significant difference between groups at any time (MMRM and ANCOVA analyses).
- Response rate (decrease of at least 30% of YMRS): no significant difference between groups neither at D21 (70% of valproate patients and 69% of lithium patients) nor at DEND (82% of valproate patients and 81% of lithium patients)
- Response rate (decrease of at least 50% of YMRS): no significant difference between groups neither at D21 (54% of valproate patients and 54% of lithium patients) nor at DEND (80% of valproate patients and 73% of lithium patients)
- Time to achieve 50% improvement in the YMRS score: no significant difference between groups (median = 21 days for the valproate patients and 21 days for the lithium patients).
- CGI-BP: no differences between treatment groups, and improvement in both groups
- Total MADRS score: low at baseline, no clinically significant change in this score over time in both groups, and no difference between groups. Less than 50% of patients received antidepressants during the course of the study. Most patients (over 60%) presented with euphoric mania at every time point (no difference between groups).

**Safety Results:**

- No difference between groups regarding the occurrence of adverse events and 56/130 (43.1%) patients in the valproate group vs 62/138 (44.9%) patients in the lithium group experienced at least one treatment emergent adverse event.
- Most frequent treatment emergent adverse events in the valproate group were nausea, reported by 13% of valproate patients and somnolence, reported by 11% of valproate patients. Most frequent treatment emergent adverse events in the lithium group were nausea and dry mouth, reported by 15% of lithium patients, and constipation and tremor reported by 12% of lithium patients.
- 8/130 (6.2%) valproate patients discontinued prematurely their treatment because of 9 adverse events (manic episode: 4, dizziness: 1, headache: 1, hypersomnia: 1, vomiting: 1, platelet count decreased: 1) vs 8/138 (5.8%) lithium patients because of 11 adverse events (manic episode: 2, aggression: 1, depression: 1, psychomotor agitation: 1, psychotic disorder: 1, dysarthria: 1, tremor: 1, nausea: 1, eyelid sensory disorder: 1, decreased appetite: 1).

- 10/130 (7.7%) valproate patients (manic episode: 5, drug toxicity: 1, injury: 1, acute sinusitis: 1, hypersomnia: 1, uterine haemorrhage: 1) and 5/138 (3.6%) lithium patients (manic episode: 4, psychotic disorder: 1) experienced at least one treatment emergent serious adverse event. Out of these serious adverse events, 2 were considered by the investigator as related to the study drug (“reasonable possibility that the adverse event was caused by the study drug”), both in the valproate group: hypersomnia (despite concomitant use of zolpidem at supratherapeutic dosage) and valproate toxicity. There were no deaths reported during the study.

**Date of the report:** 26 June 2007