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Sponsor/company: sanofi-aventis	**Clinicaltrials.gov Identifier:** NCT00431522
	Study Code: L_9387
Generic drug name: Valproate Sodium	**Date:** 19/May/2009

Title of the study:	An MRI/MRS study in patients with bipolar disease *Study code: L_9387*		
Investigator(s):	Prof. Ayşegül Özerdem, M.D. Ph.D. Dokuz Eylul University Faculty of Medicine Department of Psychiatry		
Study center(s):	Dokuz Eylul University Faculty of Medicine Department of Psychiatry		
Publications (reference):	N/A		
Study period: Date first patient enrolled: 08-Dec-2004 Date last patient completed: 15-Aug-2006		**Phase of development:** IV	
Objectives:	Primary objectives: 1. To assess regional NAA levels in drug free bipolar patients either in manic/hypomanic, or depressive or euthymic state; 2. To investigate valporate's effect on total and regional gray matter volume and NAA levels; Secondary objectives: 1. To determine the relationship between clinical improvement and image data changes in depressed or manic/hypomanic patients, 2.To assess evoked and event related potentials to visual and auditory stimuli in patients before and after valproate monotherapy in comparison to healthy controls; 3.To assess neurocognitive functioning in the same patient group before and after treatment; 4.To assess relationship between neurocognitive functions and electorphysiologic responses and to determine the topographic relationship between these findings and MR imaging findings		
Methodology:	This is a six week, open label phase IV controlled clinical trial aiming to assess magnetic resonance imaging and spectroscopy before and after six weeks of valproate monotherapy with therapeutic serum levels in patients with bipolar disorder compared to healthy controls.		
Number of patients:	Planned: 60; Selected: 58	Randomized: 30 Controls: 27	Treated: 30
Evaluated:	30	30	
Diagnosis and criteria for inclusion:	**Inclusion Criteria:** • 18-65 years old. • Diagnosis of bipolar type I or II disorder (DSM-IV) currently		

	manic/hypomanic, depressive or euthymic state based on DSM-IV criteria and YMRS=>15 for mania/hypomania and HAM-D 21=>15 for depression. • For eutyhmic patients,to be in euthymia state for at least one month medication free (except for benzodiazepines) for at least 2 weeks prior to study participation • For normal controls: no present or past psychiatric disorder as determined with a SCID-I interview and being in complete physical health as determined from medical history and physical examination. **Exclusion Criteria:** • Pregnant or planning to become pregnant or lactating patients known hypersensitivity to study drug use of any psychotropic medication except for benzodiazepines during last 2 weeks active drug or alcohol use during last 2 weeks and presence of alcohal or drug dependency during last month. • Presence of comorbid axis I conditions such as dementia, obsessive compulsive disorder and eating disorder presence of any unstable medical condition such as renal,hepatic,thyroid or hematological disease history of brain surgery presence of neurodegenerative illness or epilepcy. • Cardiac pacemaker. • Presence of ferromagnetic implanted devices or metal fragments in or near the eye or brain suicidal ideation or catatonia.
Investigational product: Dose: Administration:	Sodium Valporate 1000-2000 mg/day (serum levels 50-100 µg/mL) Oral
Criteria to stop Valproate containing regimens	NA
Duration of treatment: 6 weeks	**Duration of observation:** NA
Reference therapy: **Criteria for evaluation:**	NA
Efficacy:	• Total brain gray matter and white matter volumes, cingulated volume, dorsolateral prefrontal cortex N-acetyl aspartate (NAA) concentrations. • Young Mania Rating Scale (YMRS) and Hamilton Depression Scale (HDRS-21) scores will be used to determine clinical outcome.
Safety:	Adverse events were noted by the investigator by using "UKU side effects scale". For laboratory data: Standard hematology, blood chemistry and ECG at baseline and liver function tests and serum valproate levels (to be kept in 50-100 µg/mL range) were assessed at weeks 1,3 and 6. .
Statistical methods:	All data was analysed using SPSS program. For MR volumetric/morphometric data analysis, pretreatment data from the ROI of the patient group was compared with healthy controls by using ANCOVA where age, sex and intracranial volume were taken as covariants. Pre and posttreatment data was compared only in the patient group by using repeated measures ANCOVA. For the NAA, pretreatment peak levels and area under the curve were compared between patients and controls by using non-parametric ANOVA .

	For post-hoc analysis, groups were compared by using non-parametric t tests and in the patient group, pre and post-treatment data was compared by means of Wilcoxon test. For the secondary aims, event related potentials data was analyzed separately for each illness state by means of repeated measures ANOVA where electrode locations and hemisphere were taken as within groups, patient and control groups as between groups factors. For post-hoc analysis MannWhitney U and Wilcoxon tests were used to compare patients and controls and patients' pretreatment and posttreatment data resprectively. Parametric and nonparametric correlation tests have been used to assess relationship between laboratory changes and clinical improvement. All results are given two tailed and significance level was accepted as $p < 0.05$.
Summary:	Twenty seven patients completed the study. In the mania/hypomania group, eight patients out of nine completers met the response criteria (50 % or more reduction in YMRS scores) and four of these met the remission criteria (YMRS ≤ 8) at the end of the study. Response in the depressed group was relatively weak. Clinical data in this group is to be analysed separately. For MR spectroscopy, data from 27 patients (9 mania/hypomania, 8 euthymic, and 10 depressed) and 14 controls was available for analysis. At baseline (unmedicated), ANOVA revealed a significant difference between all patient and control groups in the right frontal NAA AUC. Post-hoc analysis showed a significant difference between both manic/hypomanic and depressives vs healthy controls whereas euthymics did not differ from healthy controls. For the post-treatment condition data from 17 patients was available for analysis. The right frontal NAA AUC measurement was still significantly different between all patient and healthy control groups. This time, the difference was caused only by the manic/hypomanic group vs healthy controls. Pre and post treatment values in the overall patient group were not significantly different. For voxel based morphometric assessments in unmedicated condition: data from 24 unmedicated patients and 19 healthy volunteers was analysed. Results revealed that bipolar patients had smaller gray matter volume in the left superior temporal gyrus (STG), left parahippocampal gyrus left dorsolateral prefrontal cortex (DLPFC) and left thalamus compared to healthy individuals. They had greater white matter volume in the right superior frontal gyrus. These findings confirm previous anatomical MRI findings suggesting the involvement of the STG, DLPFC, limbic structures and thalamus in the pathophysiology of bipolar disorder. For pre-post treatment voxel based morphometric assessments: available data from 19 patients was analysed. Pre-treatment group had smaller gray matter volume in the left amygdala, left hippocampus, right hippocampus, right anterior cingulate and left DLPFC compared to post-treatment group. This concluded that six weeks of valproate treatment at therapeutic doses led to detectable volumetric changes in bipolar patients, in the regions that are implicated in the pathophysiology of the disorder. For the secondary aims, event related oscillatory responses to visual oddball paradigm were analyzed in the euthymic and manic groups seperately in comparison to matching healthy controls both before and after six weeks of valproate treatment. Results revealed that euthymic patients had pervasive but most prominently left frontally located hyper-responsivity of the delta frequency band which represents pathology in decision making and attention functions. Valproate treatment provided reduction in this exaggerated response. Unmedicated manic patients revealed occipitally located alpha and beta frequency response disturbance representing a dysfunction in the main operating system of the brain which again improved after six weeks of valproate monotherapy. Manic patients also showed reduced right fronto-temporal coherence of the gamma frequency response pointing to a right hemisphere located disruption in the integrative functioning of brain in mania, which improved after valproate treatment. In the manic group, neither one of the improvements was correlated with the improvement in the YMRS scores. Data on neurocognitive functioning is in the process of being analyzed.

Efficacy results:	Twenty seven patients completed the study. In the mania/hypomania group, eight patients out of nine completers met the response criteria (50 % or more reduction in YMRS scores) and four of these met the remission criteria (YMRS ≤ 8) at the end of the study. Repeated measures ANOVA revealed that YMRS scores reduced significantly beginning from week 1 until week 6. Mean end of study YMRS scores were significantly lower compared to baseline values. Response in the depressed group was relatively weak. Clinical data in this group is to be analysed separately. In the euthymic group, one patient relapsed into mania during last study week.
Safety results:	Twelve different adverse events have been observed in relation with the study drug. Description of adverse events and the number of patients observed in brackets are as follow; Nausea-vomiting (6), weight gain (4), constipation (3), polyuria/polydipsia (3), sedation (3), ejaculatory dysfunction (2), palpitation (1), orthostatic dizziness (1), increased dreaming activity (2), pruritus (2), diminished sleep duration (1) and hyposalivation (1). None of these side effects reported was serious and they were overcome with dose arrangements or (for nausea) temporarily minimally additional drug applications. Drug unrelated adverse events and serious adverse events (SAE) are as follow (each by one patient); • Edema, erythema on right tibia due to trauma; not serious, radiography was taken, soft tissue injury, started to recover at next examination (1 patient). • Aggravation of depressive signs and symptoms; medical event requiring intervention; the patient was dropped out of the study (21st day, 4th visit), event was reported to the sponsor as **SAE**. The patient was administered additional antidepressant treatment (Venlafaxine HCl 75mg daily dose) and followed up. • Acute bronchitis; not serious, the patient had used drugs related with this medical condition (7th day; 2nd visit) according to a doctors prescription. • Developing psychotic symptoms; medical event requiring intervention, ziprasidon mesilat 20mg IM injection was applied, the patient was dropped out the study (21^{st}day, 4^{th} visit), the), event was reported to the sponsor as **SAE**. • Erythrocythuria; not serious; gynecology consultation was arranged; vaginitis was diagnosed and duly treated. • Hypertension; not serious; nephrology consultation was arranged; duly examinations were made as the department involved suggested; no additional problems emerged.
Date of report:	07-May-2009