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Clinical Study Summary

DEV/SGE/04125.2007

CT Registry ID#: NCT00612859
Study No.: N01086

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Based on Clinical Study Report document reference code: RRCE06F0115

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Keppra® Tablets	Levetiracetam	Social anxiety disorder (generalized type)

Name of Sponsor/Company: UCB Pharma SA

Title of Study: A multicenter, randomized, double-blind, PBO-controlled, parallel-group study to assess the efficacy and safety of levetiracetam versus PBO for the treatment of social anxiety disorder (generalized type)

Investigator(s) (number only): Not stated

Study Center(s) (number only): 20

Length of Study:		Phase of Development:	II (therapeutic exploratory)
Date first patient enrolled:	05-Sep-2003		
Date last patient completed:	15-Jun-2004		

Abstract:

The objectives of this study were to assess the efficacy and safety of levetiracetam (LEV) in social anxiety disorder (generalized type) (GSAD) during a 12-week treatment and evaluation period. Subjects were to have had a diagnosis of clinically predominant GSAD according to the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV) criteria, a score of at least 60 on the Liebowitz Social Anxiety Scale (LSAS) at Visits 1 and 2, and a Clinical Global Impression of Change (CGIC) score of >2 at Visit 2. The trial consisted of a single-blind 1-week PBO lead-in period followed by a 12-week double-blind evaluation period during which subjects were administered oral LEV 0–3000 mg/day or PBO; this consisted of 3 weeks fixed up-titration, 3 weeks flexible up-titration and 6 weeks stable dose periods. The primary efficacy end point was the change in the Liebowitz Social Anxiety Scale (LSAS) total score from Visit 2 to the last evaluation period visit attended. Secondary efficacy variables were the percent change in LSAS score from Visit 2 to the last Evaluation period visit attended; change in LSAS score from Visit 2 to each Evaluation period visit; LSAS subscale scores (fear of performance, avoidance of performance, fear of social interaction, avoidance of social interaction, total fear, total avoidance); reduction of at least 30% in LSAS score from Visit 2 to the last visit attended; CGIC score of 2 or less at the last Evaluation period visit attended; CGIC score; Hamilton Depression Rating 17 items scale (HAM-D-17 items) total and item scores; Sheehan Disability Scale (SDS) total and subscale scores (work/school, social life, family life/home responsibilities); Brief Social Phobia Scale (BSPS) total and dimension scores (fear, avoidance, physiologic distress); Massachusetts General Hospital Sexual Function Questionnaire (MGH-SF) item scores. Safety was assessed by physical examinations, vital signs, laboratory test results (including blood chemistry, hematology and urinalyses) and adverse events (AEs). The primary efficacy variable was analyzed using an analysis of covariance (ANCOVA) model, and the null hypothesis (no treatment difference) was tested using Student's t-test. Secondary efficacy variables were summarized based on observed cases (OC) and last observation carried forward (LOCF). AEs were analyzed by their frequency, severity, nature and duration.

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Number of Patients:	**PBO**	**LEV**
Planned, N:	95	95
Enrolled, N:	106	111
Single-blind, 1-week PBO lead-in	265	
Double-blind, 12-week Evaluation period	106	111
Completed, n (%):	71 (67)	77 (70)
Number of Patients Withdrawn, n (%):	35 (33)	33 (30)
Withdrawn due to Adverse Events, n (%):	6 (6)	11 (10)
Withdrawn for Other Reasons*, n (%):	29 (27)	22 (20)

*Withdrawn because of lack of efficacy, loss of efficacy, lost to follow-up, protocol violation, withdrawal of consent for personal reasons not related to AEs or lack of efficacy, other reasons, or other (change of residence)

Demography:	**PBO**	**LEV**
Gender (Females/Males):	38/68	45/65
Age (years), mean(SD):	35.77 (11.89)	35.81 (11.56)
Race, Caucasian n (%):	74 (69.8)	81 (73.6)

Safety Outcomes:

No deaths occurred during the study. One LEV subjects experienced a serious AE (SAE) during the treatment period: gastroenteritis resulting in hospitalization. No subjects in the LEV or PBO groups experienced SAEs that were considered related to treatment. Discontinuation of treatment due to AEs occurred more frequently in the LEV group (9%) than in the PBO group (5%). The most frequently occurring AEs in the dose up-titration period were nervous system disorders (headache was reported by 24.5% [LEV] and 20.8% [PBO] of subjects; somnolence was reported by 9.1% [LEV] and 8.5% [PBO] of subjects) and psychiatric disorders (insomnia and irritability were both reported by 7.3% [LEV] and 5.7% [PBO] of subjects). Fatigue (a general disorder) was reported by 10.9% (LEV) and 9.4% (PBO) of subjects. Nervous system disorders were also the most frequently reported AEs during the stable dose period, the most frequent individual AE being headache (10.9% [LEV] and 8.5% [PBO] of subjects). Similar percentages of subjects overall experienced non-psychotic mood and anxiety symptoms (17% PBO; 18.2% LEV) and sleep symptoms (8.5% PBO; 11.8% LEV). Few subjects experienced self-aggressive symptoms (0 PBO; 1.8% LEV). No clinically important differences were observed in the frequency of drug-related TEAEs: 59% (PBO) and 66% (LEV).

Treatment Emergent AEs: if applicable

Patients with at least one TEAE, n (%):	**PBO (N=106)**		**LEV (N=110)**	
Total number of TEAEs reported	367		481	
Subjects with at least one TEAE, n (%)	89 (84)		93 (84.5)	
Patients with TEAEs (≥5% of patients) (by Primary System Organ Class)	*N (%) [n considered drug-related by the Investigator]*			
Up-titration period/stable dose period	**PBO (N=106)**		**LEV (N=110)**	
	Up-titration	Stable dose	Up-titration	Stable dose
Blood and lymphatic system disorders	1 (0.9)	1 (0.9)	0	1 (0.9)
Cardiac disorders	1 (0.9)	0	1 (0.9)	0
Congenital, familial and genetic disorders	0	1 (0.9)	0	0
Ear and labyrinth disorders	1 (0.9)	0	0	0
Eye disorders	2 (1.9)	1 (0.9)	6 (5.5)	1 (0.9)
Gastrointestinal disorders	15 (14.2)	5 (4.7)	14 (12.7)	8 (7.3)
General disorders and administration site conditions	14 (13.2)	4 (3.8)	17 (15.5)	1 (0.9)
Immune system disorders	1 (0.9)	0	6 (5.5)	1 (0.9)
Infections and infestations	18 (17.0)	15 (14.2)	19 (17.3)	10 (9.1)
Injury, poisoning and procedural complications	2 (1.9)	2 (1.9)	0	1 (0.9)

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Investigations	3 (2.8)	2 (1.9)	2 (1.8)	6 (5.5)
Metabolism and nutrition disorders	4 (3.8)	0	5 (4.5)	0
Musculoskeletal and connective tissue disorders	4 (3.8)	5 (4.7)	6 (5.5)	6 (5.5)
Nervous system disorders	35 (33.0)	13 (12.3)	48 (43.6)	19 (17.3)
Psychiatric disorders	22 (20.8)	8 (7.5)	29 (26.4)	13 (11.8)
Renal and urinary disorders	1 (0.9)	1 (0.9)	0	0
Reproductive system and breast disorders	4 (3.8)	3 (2.8)	6 (5.5)	2 (1.8)
Respiratory, thoracic and mediastinal disorders	15 (14.2)	2 (1.9)	11 (10.0)	3 (2.7)
Skin and subcutaneous tissue disorders	7 (6.6)	1 (0.9)	3 (2.7)	3 (2.7)
Vascular disorders	0	1 (0.9)	0	0
Death, SAEs, and Other SAEs: if applicable				
Death, n (%):	0		0	
Patients with SAEs, n (%):	0		1 (0.9)	
Patients with SAEs *(by Primary System Organ Class)*	*N (%) [n considered drug-related by the Investigator]*			
Gastroenteritis	0		1 (0.9) [0]	

Primary & Secondary Outcomes:
Substantial improvements in mean LSAS scores from Visit 2 to Visit 11 were observed in both treatment groups. Mean LSAS scores at Visit 2 and Visit 11 (LOCF) for the PBO group were 93.2 and 62.4; corresponding scores for the LEV group were 91.0 and 65.7. Adjusted mean changes (Visit 2 to Visit 11 [LOCF] for the PBO and LEV groups were -28.71 and -24.44. The difference between these adjusted change scores, showing a trend in favor of PBO treatment, was below the pre-determined 10-point limit signifying clinical importance and was not statistically significant (ANCOVA for treatment effect p=0.282). A non-parametric test of change from Visit 2 to Visit 11 (LOCF) using the Wilcoxon Signed Rank test showed no difference between PBO and LEV groups (p=0.103). The ANCOVA treatment effect was the prospectively determined primary outcome measure and did not achieve the required statistical α value of 0.05.

Publication Reference(s) based on the study: None

Date of report: 6-Nov-2006