N01142, 2004-001302-27

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB S.A. – Pharma Sector

Chemin du Foriest

1420 Braine-l'Alleud

Belgium

Official study title:

An 8-week exploratory, double-blind, placebo controlled randomized trial: Evaluation of the efficacy and safety of levetiracetam up to 3000 mg/day (250-500 mg oral tablets in b.i.d. administration) on neurolepticinduced tardive dyskinesia in subjects with stable axis I psychiatric disorder, aged from at least 18 years to 80 years

2. SYNOPSIS

Name of Sponsor/Company: UCB S.A. – Pharma Sector Belgium	Individual Study Table Referring to Module 5.3.4.2	*(For National Authority Use only)*
Name of Finished Product: Keppra®	Volume:	
Name of Active Ingredient: Levetiracetam	Page:	

Title of Study:
An 8-week exploratory, double-blind, placebo controlled randomized trial: Evaluation of the efficacy and safety of levetiracetam up to 3000 mg/day (250-500 mg oral tablets in *b.i.d.* administration) on neuroleptic-induced tardive dyskinesia in subjects with stable axis I psychiatric disorder, aged from at least 18 years to 80 years.

Investigator(s):
15 Investigators were involved in randomizing patients.

Study Center(s):
15 centers screened and randomized patients in 5 [redacted] countries: [redacted] (2 centers / 6 patients randomized), [redacted] (5 centers / 30 patients randomized), [redacted] (4 centers / 12 patients randomized), [redacted] (2 centers / 5 patients randomized) and [redacted] (2 centers / 17 patients randomized).

Publication:
None at the date of the present report.

Studied Period (years): First patient screened: 12-May-2005 Last patient completed: 29-Dec-2005	Therapeutic exploratory trial (Phase II))

Objectives:
Primary objective:
- Compare the efficacy of levetiracetam (250 mg to 1500 mg *b.i.d.*) to placebo, in neuroleptic-induced tardive dyskinesia in patients with a stable axis I psychiatric disorder.

Secondary objectives:
- Compare the efficacy of levetiracetam (250 mg to 1500 mg *b.i.d.*) to placebo in neuroleptic-induced akathisia and other extrapyramidal symptoms in patients with a stable axis I psychiatric disorder.
- Evaluate the effect of levetiracetam (250 mg to 1500 mg *b.i.d.*) compared to placebo, on the primary psychiatric disorder.
- Evaluate the safety of levetiracetam.

Methodology:
Multicenter, double-blind, randomized, placebo-controlled, parallel group design.

Number of Subjects:
74 patients were screened and 70 randomized

Diagnosis and Main Criteria for Inclusion:
- Men and women of non-childbearing potential between the ages of 18 and 80 who meet DSM IV criteria for **stable Axis I psychiatric disorder** since at least 6 months prior to the screening visit (V1) and do not suffer from any Axis II condition since the last 6 months prior to the screening visit (V1).
- Patients who meet the DSM-IV criteria for stable **neuroleptic-induced tardive dyskinesia** (NITD) since at least 1 month prior to screening and presenting with a total mean hyperkinesia score of at least 5 on the St Hans Rating Scale (SHRS) at screening visit (V1) and at baseline visit (V2) (evaluated by the Investigator).

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- Patients on **antipsychotic treatment** for at least 6 cumulative months prior to the screening visit (V1), and if on antipsychotic treatment at screening (V1), the patient ought to be on a stable dose regimen since at least one month.

Test Product:	**Dose and Mode of Administration:**	**Batch Number(s):**
Levetiracetam film-coated tablets of 250 or 500 mg	Oral administration of 250 mg to 1500 mg *b.i.d.*	250 mg: [redacted] (*) 500 mg: [redacted] (**)

Duration of Treatment:
The time span between screening visit and final visit accounts for 11 weeks. The successive study periods are as follows: 1-week baseline period / 8-week treatment period (4-week uptitration and 4-week stable dose) / 2-week downtitration → drug free period.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number(s):**
Matching placebo tablets	*b.i.d.* oral administration	[redacted] (*) (**)

Criteria for Evaluation:
Efficacy:
The primary efficacy variable is the change from baseline on the total mean score of hyperkinesia (using the scores of the hyperkinesia subscale of the St Hans rating scale / STHS) estimated at the evaluation visit (V6) as evaluated by an independent blinded central reviewer [redacted].
The secondary efficacy variables that were analyzed are:

- The change from baseline in the total mean score of hyperkinesia (using the STHS hyperkinesia subscale) estimated at the evaluation visit (V6) as evaluated by the Investigator.
- The percentage reduction from baseline in the total mean score for hyperkinesia (hyperkinesia subscale of the STHS) estimated at the evaluation visit (V6) as evaluated by the independent blinded central reviewer.
- Patients with a decrease of at least 50% on the total mean score of hyperkinesia estimated at the evaluation visit (V6) as evaluated by the independent blinded central reviewer.
- The change from baseline in Global Score on each individual SHRS subscale (independent blinded central reviewer). This applies to the hyperkinesia subscale, the Parkinsonism subscale and the dystonia subscale.
- The change from baseline in mean score on the individual SHRS items (independent blinded central reviewer). This applies to the Parkinsonism subscale and the akathisia subscale.
- Time evolution (including change from baseline) of the brief psychiatric rating scale / BPRS.
- Investigator's Global Evaluation Scales (GESs); one on the patient's neuroleptic induced tardive dyskinesia (NITD) and one on the underlying illness.
- Graphical comparison of the primary efficacy variable and the change from baseline in the total mean score of hyperkinesia (using the STHS hyperkinesia subscale) estimated at the evaluation visit (V6) as evaluated by the Investigator.

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Name of Finished Product: Keppra®	Volume:	
Name of Active Ingredient: Levetiracetam	Page:	

Safety:

Safety Variables

Adverse events (AEs), laboratory tests, physical and neurological examinations, vital signs, body weight and Electrocardiogram (ECG).

Statistical Methods:

Study populations:

The intention-to-treat population (ITT) consists of all randomized subjects who took at least one dose of study medication.

The Per-Protocol (PP) population consists of all subjects in the ITT population without major protocol violations that affect the primary efficacy variable (total mean score of hyperkinesia in the St Hans rating scale).

The safety and efficacy analyses are solely based on the intention-to-treat (ITT) population.

Since the percentage of patients with protocol violations affecting the primary endpoint was 5.7%, the primary efficacy analysis was not conducted on the PP population as it would have been done if this percentage had exceeded 10%.

Hypothesis testing is being performed only on the primary efficacy variable. The statistical test is two-sided and p-values less than 5% are considered statistically significant. The statistical evaluation uses a linear mixed model for longitudinal data.

For to the secondary efficacy variables, the difference between the treatment groups is estimated from the data, using descriptive statistics. Inferential statistics are applied for the assessment of responders (patients with a decrease of at least 50% on the total mean score of hyperkinesia in the SHRS at the evaluation visit), and for the assessment of the global evaluation scales (GESs).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

		V6 (evaluation visit)	**PBO**	**LEV**	**p-value**
1ary efficacy	SHRS/Hyperkinesia (1)	Baseline value – mean (SD)	5.60 (4.33)	6.51 (4.51)	
		Change from baseline total mean score – independent rater mean (SD)	- 0.34 (1.87)	- 0.21 (1.79)	0.655
2ary efficacy	SHRS/Hyperkinesia (2)	Baseline value – mean (SD)	15.21 (6.92)	13.65 (6.03)	
		Change from baseline total mean score – Investigator mean (SD)	- 5.73 (6.92)	- 4.31 (6.03)	NT

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Name of Finished Product: Keppra®	Volume:	
Name of Active Ingredient: Levetiracetam	Page:	

	SHRS/Hyperkinesia (3)	Baseline value – mean (SD) % reduction from baseline on total mean score – independent rater mean (SD)	5.60 (4.33) 7.97 (47.33)	6.51 (4.51) 0.64 (48.62)	 NT
	SHRS/Hyperkinesia (4)	Patients with a decrease of ≥ 50% on total mean score (responder rate) – independent rater mean (SD)	5 (17.9%)	5 (16.1%)	0.930
	SHRS/Hyperkinesia (5)	Baseline value – mean (SD) Change from baseline global score – independent rater mean (SD)	1.54 (1.07) - 0.17 (0.65)	1.65 (0.98) - 0.09 (0.58)	 NT
	SHRS/Parkinsonism (6)	Baseline value – mean (SD) Change from baseline global score – independent rater mean (SD)	1.26 (0.85) - 0.03 (0.49)	1.18 (0.72) - 0.06 (0.35)	 NT
	SHRS/Dystonia (7)	Baseline value – mean (SD) Change from baseline global score – independent rater mean (SD)	1.34 (0.87) 0.03 (0.49)	1.53 (0.86) 0.00 (0.50)	 NT
	SHRS/Parkinsonism (8)	Baseline value – mean (SD) Change from baseline mean score – independent rater mean (SD)	1.00 (0.61) - 0.13 (0.22)	0.98 (0.45) - 0.11 (0.32)	 NT
	SHRS/Akathisia (9)	Baseline value – mean (SD) Change from baseline mean score – independent rater mean (SD)	1.62 (1.14) - 0.11 (0.81)	1.71 (1.40) - 0.33 (1.19)	 NT

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	BPRS (10)	Baseline value – mean (SD)	36.90 (11.27)	39.10 (13.58)	
		Change from baseline score mean (SD)	- 4.98 (5.99)	- 2.63 (6.41)	NT
	GES NITD (11)	Marked or moderate improvement [no. (%) patients]	13 (43.3%)	8 (24.2%)	0.111
	GES underlying psychiatric illness (12)	Marked or moderate improvement [no. (%) patients]	6 (20.0%)	2 (6.1%)	0.100

NT = no inferential analysis performed

SAFETY RESULTS:

(1) Adverse events:
Overall Summary of Treatment-Emergent Adverse Events during the Evaluation Period and the Down-titration Period – ITT Population

	Evaluation period		**Down-titration**	
	PBO (N = 35) n (%)	**LEV (N = 34)** n (%)	**PBO (N = 35)** n (%)	**LEV (N = 34)** n (%)
Total number of TEAEs	34	16	5	2
Patients with at least one TEAE	16 (45.7%)	8 (23.5%)	5 (14.3%)	2 (5.9%)
Patients with TEAEs leading to permanent study drug discontinuation	4 (11.4%)	1 (2.9%)	1 (2.9%)	0
Patients with drug-related TEAEs	9 (25.7%)	5 (14.7%)	2 (5.7%)	0
Patients with severe TEAEs	3 (8.6%)	0	1 (2.9%)	0
Patients with serious TEAEs	1 (2.9%)	0	0	0
Number of deaths	0	0	0	0

Across all SOCs, the number of patients with at least one specific TEAE was comparable in both treatment groups.
The number of patients with AEs in the psychiatric disorders SOC was comparable in both treatment groups. Within the psychiatric disorders SOC, psychotic disorder, schizophrenia and bipolar I disorder were reported once each in PBO patients; all events were a worsening of pre-existing conditions related to the underlying illness of the patients.

(2) No noteworthy concerns arose from the N01142 hematology and blood biochemistry results, vital signs and body weight monitoring, physical and neurological follow up and ECG monitoring.

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Name of Finished Product: Keppra®	Volume:	
Name of Active Ingredient: Levetiracetam	Page:	

CONCLUSIONS:

From the results of the present placebo controlled parallel group exploratory 8-week study in 70 patients with stable axis I psychiatric disorder, there appears to be no therapeutic benefit of LEV 1500 mg *b.i.d*. in neuroleptic-induced tardive dyskinesia.

From the global evaluation of the primary psychiatric illness, there also appears to be no influence of LEV on the underlying psychiatric disorder.

Hyperkinesia ratings (SHRS) from the independent rater were consistently lower than the Investigator ratings. However, the changes from baseline within each treatment group were of similar magnitude.

	Independent rater		**Investigator**	
	PBO	**LEV**	**PBO**	**LEV**
Baseline value – mean (SD)	5.60 (4.33)	6.51 (4.51)	15.21 (6.92)	13.65 (6.03)
Change from baseline total mean score – mean (SD)	- 0.34 (1.87)	- 0.21 (1.79)	- 5.73 (6.92)	- 4.31 (6.03)

Therefore, it is likely that the independent rater would not have included almost half of the patients based on the inclusion criteria of the total mean hyperkinesia score to be at least 5 on the St Hans rating scale.

Safety assessments did not reveal any point of particular concern. The triad somnolence / asthenia / dizziness was not more frequently reported in the LEV as compared to PBO patients and neither nervous nor psychiatric adverse events were more frequent in the LEV patients.

Report Date:
25-Jul-2006