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: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Title of Study:
A placebo-controlled, single blind, multi-center study to explore the photoparoxysmal response in photosensitive epileptic subjects after one single oral dose (20 to 600 mg) of ucb 34714 in capsules.

N.B. According to the positive results observed during the study with the lowest doses of ucb 34714 foreseen in protocol, it was decided to also investigate the effect of a single oral dose of 10 mg of ucb 34714 (protocol amendment 6).

Investigator(s):
Coordinating Investigator:
- [redacted], MD, NL-1815 JD Alkmaar.

Investigators who selected at least 1 subject were:
- [redacted], MD, D-77694 Kehl-Kork.
- [redacted], MD, F-67091 Strasbourg.
- [redacted], MD, F-76031 Rouen.
- [redacted], MD, F-94270 Kremlin Bicêtre.
- [redacted], MD, F-13385 Marseille.

Study Center(s):
Centers where at least 1 subject was selected were:
- Epilepsiezentrum Kork; 1 Landstraβe, D-77694 Kehl-Kork, Germany.
- CHRU – Hôpital Civil; 1 place de l'Hôpital, F-67091 Strasbourg, France.
- Hôpital CHU Charles Nicolle; 1 rue de Germont, F-76031 Rouen, France.
- Hôpital CHU de Bicêtre; 78 rue du Général Leclerc, F-94270 Kremlin Bicêtre, France.
- Hôpital de la Timone AP-HM; 254 rue Saint-Pierre, F-13385 Marseille Cedex, France.

Publication:
None.

Studied Period (years): 13-Sep-2002 26-Jun-2003	**Phase of Development:** Clinical pharmacology / Phase IIa.

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: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Objectives:

The primary objective of the study was to identify the lowest single oral dose of ucb 34714 producing maximum diminution or suppression of the photoparoxysmal EEG response (PPR) evoked by intermittent photic stimulation (IPS) in photosensitive epileptic subjects. This was assessed by the standard photosensitivity range (SPR).

The secondary objectives were:

- To assess the relationship between plasma concentrations of ucb 34714 and changes in the photosensitivity frequency range.
- To assess the relationship between plasma concentrations of ucb 34714 and time of onset and duration of the suppressing effect.
- To document the safety of ucb 34714 in epileptic subjects.
- To explore the possible pharmacokinetic interactions between ucb 34714 and concomitant anti-epileptic drugs (AEDs).
- To gain information on possible effects of ucb 34714 on mood in epileptic subjects assessed through standardized questionnaires (POMS, and ARCI-49).

Methodology:

This was a placebo-controlled, single blind, single period, multi-center study conducted in photosensitive epileptic subjects, with or without concomitant anti-epileptic medications.
Study drugs were administered around 8:00 on the first day (placebo) and on the second day (ucb 34714).
The starting dose of ucb 34714 to be tested in the first 4 subjects was 80 mg. This dosage was to be subsequently reduced or increased according to pharmacodynamic and safety results.

Number of Subjects:

Amongst the 26 subjects screened, 19 were enrolled and completed the study.

Diagnosis and Main Criteria for Inclusion:

- Males or Females aged 18 - 60 years on signature of IEC approved Informed Consent.
- Epileptic subjects with or without concurrent seizures as long as the seizure frequency and type were not interfering with the conduct of the study.
- Subjects who previously exhibited a generalized PPR on routine EEG investigation (i.e. generalized epileptiform discharges with or without a focal onset and outlasting the IPS stimulus train).
- Subjects showing a clear and consistent photosensitivity range in at least one eye condition as confirmed at screening and pre-dose (Day-1).
- For subjects under concomitant anti-epileptic medications, dosage and timing of intake of the anti-epileptic medications stable during at least the 4 weeks before ucb 34714 dosing.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
ucb 34714	10 mg oral capsule	12291
	20 mg oral capsule	11808
	40 mg oral capsule	11809
	80 mg oral capsule	11810
	150 mg oral capsule	11811

Duration of Treatment:

Duration of study from selection to discharge visits was, at the most, 26 days per subject. Every subject was administered a single dose of placebo and a single dose of ucb 34714.

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: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Reference Therapy: Placebo	**Dose and Mode of Administration:** 10, 20, 40, and 80 mg oral capsules 150 mg oral capsule	**Batch Number:** 11758 11746

Criteria for Evaluation:

Pharmacodynamic parameters:

The Standard Photosensitive Range (SPR) was the main parameter to identify the lowest single oral dose of ucb 34714 producing maximal diminution or suppression of the intermittent photic stimulation (IPS) evoked photoparoxysmal EEG response (PPR) in photosensitive epileptic subjects. SPR was defined as the number of frequencies (steps) between the lowest and highest frequencies which consistently elicited a photoparoxysmal response (frequencies used were: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, and 60 Hz). SPR was assessed in 3 distinct eye conditions: eye-opened, eye-closed, and eye-closure (eyes closed after IPS initiation). Results assessed in "eye-closure" condition were considered as the most relevant.

Besides, Profile Of Mood State (POMS) and Addiction Research Center Inventory short form questionnaire (ARCI-49) were administered to investigate the effects of ucb 34714 on mood in photosensitive epileptic subjects.

Pharmacokinetics parameters:

PK parameters of ucb 34714 were computed from the blood samples collected up to 72 hours post-dose. Main PK parameters were: AUC(0-t), AUC, C_{max}, t_{max}, λ_z, and $t_{½}$.

Safety:

Safety was assessed through vital signs, physical examination, laboratory results (hematology, biochemistry, urinalysis), 12-lead ECG, and adverse events.

Statistical Methods:

Pharmacodynamic parameters were analyzed using descriptive statistics by dose, eye condition and time-point. Graphical displays of the raw-data were performed.
Plasma concentrations and pharmacokinetic parameters of ucb 34714 respectively measured and computed for every subject were summarized and presented by dose using descriptive statistics.
Descriptive statistics were used to analyze the safety parameters assessed during the study. Shift tables were produced to describe modifications in the laboratory results.

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: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

SUMMARY – CONCLUSIONS

Nineteen Caucasian subjects (15 females, 4 males) with a mean age (±SD) of 25.8 (±9.1) years were enrolled and completed the study.

Pharmacodynamic results:

- SPR.

According to the positive results observed during the study with the lowest doses of ucb 34714 foreseen in protocol, it was decided to also investigate the effect of a single oral dose of 10 mg of ucb 34714 (protocol amendment 6).
Descriptive statistics (median (range)) of SPR changes from pre-dose in "eye-closure" condition are given in the table below (Per protocol population).

Drug	Time	10 mg n = 4	20 mg n = 5	40 mg n = 5	80 mg n = 4
Placebo	0.5 h	-1 (-7; 1)	1 (-3; 3)	-1 (-3; 2)	1 (-2; 1)
	1 h	-1 (-4; 1)	0 (-1; 3)	-1 (-3; 1)	0 (-2; 2)
	2 h	1 (-6; 4)	-1 (-1; 3)	0 (-3; 3)	1 (-2; 1)
	4 h	3 (-1; 5)	0 (-2; 1)	0 (-4; 2)	1 (-3; 2)
	6 h	2 (-1; 5)	1 (0; 3)	-1 (-2; 1)	2 (-2; 3)
	8 h	1 (-2; 4)	0 (-3; 5)	1 (-2; 2)	0 (-2; 2)
ucb 34714	0.5 h	-6 (-8; 0)	-8 (-12; 4)	-3 (-7; -1)	-8 (-13; -6)
	1 h	-8 (-10; -5)	-8 (-12; 5)	-7 (-8; -5)	-8 (-13; -6)
	2 h	-7 (-9; -5)	-8 (-12; 3)	-7 (-8; -4)	-8 (-13; -6)
	4 h	-8 (-9; -4)	-8 (-12; -1)	-4 (-8; -1)	-7 (-13; -2)
	6 h	-5 (-8; -3)	-5 (-8; 0)	-5 (-10; -3)	-7 (-13; -3)
	8 h	-6 (-10; 5)	-8 (-12; -1)	-6 (-7; -5)	-8 (-13; -6)

Almost no SPR changes from pre-dose in "eye-closure" condition were observed after placebo. Important SPR changes or even complete abolishment of the photosensitivity windows were observed after ucb 34714 administration no matter the dose used.

Descriptive statistics (N, Median (range)) for time to first response and duration of response in "eye-closure" condition are given in the table below. Response was defined as a SPR change of at least 3 steps.

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Name of Finished Product: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Parameter	Drug	Dose	N[(a)]	Median (Range)
Time to first response (h)	Placebo	10 mg	1	0.5 (0.5; 0.5)
		20 mg	2	4.3 (0.5; 8.0)
		40 mg	4	1.5 (0.5; 4.0)
		80 mg	1	4.0 (4.0; 4.0)
	ucb 34714	10 mg	4	0.5 (0.5; 1.0)
		20 mg	4	0.5 (0.5; 1.0)
		40 mg	5	0.5 (0.5; 1.0)
		80 mg	4	0.5 (0.5; 0.5)
Duration of response (h)	Placebo	10 mg	1	1.5 (1.5; 1.5)
		20 mg	2	0.0 (0.0; 0.0)
		40 mg	4	0.0 (0.0; 0.5)
		80 mg	1	0.0 (0.0; 0.0)
	ucb 34714	10 mg	4	29.3 (7.5; 31.5)
		20 mg	4	27.5 (23.0; 31.5)
		40 mg	5	27.0 (23.5; 47.5)
		80 mg	4	59.5 (27.5; 71.5)

[(a)] Number of subjects who had a response.

Median time to first response was 0.5 h after ucb 34714 administration no matter the dose used. Median duration was around 28 h after 10, 20 or 40 mg of ucb 34714. Median duration was longer after 80 mg of ucb 34714 (59.5 h). Fewer subjects were responders under placebo and the duration of response was mostly restricted to one time point.
Aside from these results, time to maximal reduction in SPR was dose related: 1.5, 1.0, 1.0 and 0.5 hours after respectively 10, 20, 40 and 80 mg of ucb 34714.

- **POMS**

After ucb 34714, no relevant changes in the 6 POMS sub-scales and in the total mood disturbance score were observed.

- **ARCI-49**

Three hours after ucb 34714 intake, no relevant changes were observed in 4 of the ARCI-49 sub-groups. A median increase of 3 units of score was observed in the pentobarbital-chlorpromazine-alcohol group (sedation) after 80 mg of ucb 34714.

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Name of Finished Product: Not available	Volume:	
Name of Active Ingredient: ucb 34714	Page:	

Pharmacokinetic results

Plasma levels of ucb 34714 reached a peak approximately 2.0 hours (median time) following administration. Half-life time ($t_{1/2}$) was about 8.5 hours. These findings are consistent with those reported in healthy subjects (t_{max}: around 2 h, $t_{1/2}$: between 7 and 8 hours).

Pharmacokinetic / pharmacodynamic relationship
No obvious relationship between pharmacodynamic activity of the drug (expressed as AUEC, SPR change or duration of response) and the dose or the exposure to the drug (expressed as AUC or Cmax) was found. The 80 mg dose appeared more efficient (time to maximal response, duration of response) in reducing the photosensitivity than the other doses.

SAFETY RESULTS:

Twelve subjects out of 19 reported 20 AEs during the study (4 after placebo, 16 after ucb 34714). All the AEs reported but one (somnolence after 20 mg placebo) were mild to moderate. All the AEs reported but one (dry mouth after 40 mg ucb 34714) were resolved at the end of the study.
No specific association between the AEs reported after ucb 34714 and the dosage used was observed. Five subjects reported dizziness, 3 reported somnolence.
No clinically relevant findings were observed in vital signs, ECG, physical examination, laboratory results during the study. No serious AEs occurred
In the present study, single doses (10 mg, 20 mg, 40 mg, and 80 mg) of ucb 34714 were [redacted] and well tolerated.

CONCLUSIONS:

All the single doses (10, 20, 40, and 80 mg of ucb 34714) administered in the present study were effective in reducing or even abolishing the photoparoxysmal EEG response in photosensitive epileptic subjects. All doses were [redacted] and well tolerated. Eighty mg of ucb 34714 was however the most efficient dosage.

Report Date:
31-Mar-2004