C32322, 2006-002204-33

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB Pharma S.A.

Chemin du foriest

1420 Braine-l'Alleud

Belgium

Official study title:

Double-blind, placebo-controlled, randomized, parallel-group Phase II study in subjects with relapsing forms of multiple sclerosis (MS) to evaluate the safety, tolerability, and effects of two doses of CDP323 over 24 weeks with a rater-blind MRI follow-up over 12 weeks

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Name of company: UCB Pharma S.A. UCB Inc,	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: CDP323	**Volume:** Not applicable	
Name of active ingredient: CDP323	**Page:** Not applicable	

Title of study: Double-blind, placebo-controlled, randomized, parallel-group Phase II study in subjects with relapsing forms of multiple sclerosis (MS) to evaluate the safety, tolerability, and effects of two doses of CDP323 over 24 weeks with a rater-blind MRI follow-up over 12 weeks.

Investigator(s): Seventy Investigators screened subjects in the study.

Study site(s): Seventy sites participated in the study.

Studied period: 80 Weeks **First subject enrolled:** 04 May 2007 **Last subject completed:** 28 Jul 2010	**Phase of development:** Phase 2

Objective(s): The primary objective of this study was to compare the effects of CDP323 500mg once daily and twice daily on MS-related imaging parameters in subjects with relapsing multiple sclerosis with the effects seen under placebo treatment in that population over a period of 24 weeks.
Secondary objectives were to investigate the effect of CDP323 500mg once daily and twice daily on occurrence of relapses, as well as the investigation of safety and tolerability of CDP323 and pharmacokinetic (PK) parameters and its metabolites.

Methodology: Subjects were assessed for eligibility during a 4-week Screening Period. At the end of the Screening Period, eligible subjects were randomized to 1 of 3 treatment arms (CDP323 500mg; CDP323 1000mg [given as 500mg twice daily]; or placebo). After randomization, subjects entered directly into a 24-week double-blind Treatment Period. Contrast-enhanced magnetic resonance image (MRI) scans were obtained at Screening, Baseline, and every 6 weeks thereafter. After the Treatment Period, subjects underwent a rater-blinded 12-week Drug-Free Follow-Up (FU) Period. All treated subjects, were asked to participate in a FU Visit 12 months after the last intake of study drug.

Number of subjects (planned and analyzed): A total of 222 subjects (74 subjects per treatment group) were planned and 234 subjects were analyzed.

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Diagnosis and main criteria for inclusion:
Main inclusion criteria:

- Relapsing form of multiple sclerosis
- Screening expanded disability status scale (EDSS) score 0 to 6.0, inclusive
- At least 1 clinical relapse in the last 12 months before Screening and documented in the patient medical record
- Active disease, defined by a set of MRI activity criteria
- Failed prior treatment with beta-interferons or glatiramer acetate

Main exclusion criteria:

- Signs of silent infections including positive tests for Human Immunodeficiency Virus 1 (HIV), HIV2, or hepatitis B or C or Tuberculosis (TB)
- Known allergy to gadolinium-di-ethylene triamine pentaacetate (gd-DTPA), and/or ingredients of the study drug formulation
- Pretreatment with immunosuppressive or immunomodulatory drugs prior to Screening within certain timeframes

Test product, dose(s) and mode of administration, batch number(s): CDP323 was administered orally and was given as hard-gelatin capsules containing 250mg of drug substance (batch numbers [redacted] and [redacted]).

Duration of treatment:

Arm 1:	CDP323 500mg given orally in 2 capsules at 250mg as a morning dose each day over 24 weeks and placebo given orally as 2 matching capsules as an evening dose each day over 24 weeks
Arm 2:	CDP323 1000mg given orally in 4 capsules at 250mg (2 capsules in the morning and 2 capsules in the evening) each day over 24 weeks
Arm 3:	Placebo given orally as 4 capsules (2 capsules in the morning and 2 capsules in the evening) each day over 24 weeks

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo was provided as a matching hard-gelatin capsule for each of the 2 CDP323 dosages (batch numbers [redacted], and [redacted]

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Criteria for evaluation:

Efficacy: Magnetic resonance image scans were performed with gd-DTPA (Magnevist®; 0.3mmol/kg).

Pharmacokinetics/pharmacodynamics: Plasma concentrations of CDP323, CT7758, and CT533652-00 were determined. Time-course of lymphocyte phenotyping (CD3, CD4, CD8, CD19, and CD25) was measured.

Safety: Safety measurement included adverse events (AEs); clinical laboratory parameters (hematology, biochemistry, and urinalysis); pregnancy testing; testing for HIV, hepatitis, tuberculosis, toxoplasmosis, and human polyomavirus (JC) viral deoxyribonucleic acid. (surveillance for progressive multifocal leukoencephalopathy [PML]); electrocardiogram (ECG); vital signs; physical and neurological examinations, EDSS; and MRI.

Statistical methods: The Intention-to-Treat (ITT) population included all randomized subjects. The Completer Set (CS) consisted of subjects who completed the Treatment Period (ie, they performed Visit 14 rather than Visit 14 Early Termination) and who satisfied the following criteria:

- Stable triple or stable low-dose gd
- No post-Baseline scan missing
- No exposure to systemic steroid treatment within 7 days prior to a post-Baseline MRI
- Visit 14 scan was available and under exposure of study drug (at latest 7 days after last drug intake)

Although the treatment was terminated prematurely, analyses of the CS was maintained in order to eliminate any influence of missing data or invalid MRI scans.

The Safety Set (SS) consisted of all subjects to whom study drug was dispensed.

The primary efficacy variable was the cumulative number of newly active lesions over 24 weeks as seen on standardized brain MRI scans and was analyzed using the ITT and CS populations.

The Baseline MRI scan was done at Screening (Visit 1), at Baseline (Visit 3); post-Baseline at Visit 8, Visit 10, Visit 12, and Visit 14 including Visit 14 Early Termination (Treatment) and Visit 16 and Visit 17 (12-Week Drug-Free FU).

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A post-Baseline scan was considered valid, if

- It was performed under the same gd dose as the scan at Visit 8 and
- If it was performed at the same gd dose as the preceding scan;
- The subject did not receive systemic steroids within 7 days prior to the scan, and
- The scan does not refer to a scan that was done under exposure of systemic steroids (within 7 days prior to the scan).

All criteria needed to be satisfied.

Magnetic resonance image scans may have been rejected by the image analysis center (IAC) due to quality issues. That would mean that the MRI scan was either repeated at a later time point or that MRI variables were not available, if the scan was not repeated.

Furthermore, MRI scans may have been missing for any other reason, eg, a subject discontinued prematurely before Visit 14. As already mentioned, for analysis, Visit 14 Early Termination was assigned to the proper visit based on predefined visit windows. Re-assignment was done before deriving the MRI variables described in this section.

The following approaches were applied to account for invalid or missing MRI scans:

- Method 1:
  Missing or invalid post-Baseline assessments were imputed by the individual mean over nonmissing valid post-Baseline assessments. If no valid post-Baseline assessment was available, the mean of the respective treatment group at the specific visit was used.
- Method 2:
  A subject was taken into account until the first occurrence of a missing or invalid MRI assessment. If no valid post-Baseline assessment was available, the subject was not considered in the analysis.

The mean of the respective treatment group at the specific visit (Method 1) was calculated based on valid scans.

In case of imputing observations with either the individual mean or the mean over a certain treatment group, the number of lesions was not necessarily an integer. For a presentation in categories (0, 1, 2, 3, 4 to 6, 7 to 9, 10 to 12; where applicable), numbers were rounded (mathematical approach).

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The derivation of the MRI variables at each Post-Baseline Visit was based on both methods. Since burden of disease, black holes, and brain volume were assessed only once after Baseline, no specific handling was applied for these variables in case of missing or invalid scans.

- Method 3:
  In addition, cumulative number of new gd enhancing lesions on T1, cumulative number of new T2 lesions, cumulative number of enlarging T2 lesions, number of newly active lesions per visit and cumulative number of newly active lesions were also derived using the following approach:
  - The gd dosage was not taken into consideration for assessing a scan as being valid or invalid. Scans were considered for the analysis without applying an imputation rule, whatever gd dosage was used.
  - Scans that were considered invalid due to any other reason (for example due to exposure to steroids), and missing scans were imputed according to Method 1.

Summary and conclusions

Subject disposition: A total of 335 subjects were screened for the study, and 234 subjects were randomized. Overall 138 subjects (59%) completed the study. A total of 96 randomized subjects (41%) discontinued from the study. The most common reasons for discontinuation was following Independent Data Monitoring Committee recommendation 60 subjects (25.6%) and adverse event(s) 22 subjects (9.4%).

A total of 109 subjects were included in the CS, and 234 subjects were included in the SS. A greater number of discontinued subjects in the CDP323 1000mg/day arm was reflected in the lower number of subjects in the CS in this treatment group.

Efficacy results: The primary efficacy variable was the cumulative number of newly active lesions over 24 weeks as observed on standardized brain MRI scans for the ITT population. The following summarizes the efficacy conclusions for the ITT population:

- The median cumulative number of newly active lesions by the end of treatment (EOT) as compared to Baseline was the same across all treatment groups. No statistically significant difference was observed between placebo and each of the CDP323 treatment groups.

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- The median cumulative volume (mm3) of gd enhancing lesions on T1 MRI scans by Week 28/EOT was similar across all treatment groups (placebo [198.00], CDP323 500mg/day [180.00], and CDP323 1000mg/day [161.00]).
- The median volume (mm3) of hypertensive lesions on T2 MRI scans at the EOT was the lowest in the placebo (3128.5) compared with the CDP323 500mg/day (6648.0) and CDP323 1000mg/day (3471.0) treatment groups.
- The median percent change from Baseline in normalized brain volume (cm3) was similar in the placebo (-20.5%) and the CDP323 500mg/day (-23.5%) treatment groups and greater in the CDP323 1000mg/day (-38.0%) treatment group.
- The incidence of activity-free scans by Week 28/EOT and the median proportion of "active" post-Baseline MRI scans were similar across treatment groups.
- Across all treatment groups, the incidences of relapses were similar; the majority of subjects had no confirmed relapses, and no subject had ≥3 relapses. In addition, the total treatment duration in subject-years was similar among treatment groups, and median annual relapse rates were the same.

In conclusion, there was not statistical evidence of differences between treatment groups that was consistent throughout all the efficacy parameters measured. Similar lack of efficacy was observed upon interim analysis, which resulted in premature study termination. While there appeared to be some benefit in the highest dose group, this was clearly not near the magnitude expected of an α-4 integrin inhibitor.

Pharmacokinetics/pharmacodynamics results: CDP323 plasma concentrations were very low compared to the 2 metabolites, CT7758 and CT533652-00 plasma concentrations. CT533652-00 showed the highest plasma concentrations

For the 3 analytes, the plasma concentrations were similar between the CDP323 500mg/day and CDP323 1000mg/day groups.

The high variability observed in the plasma concentrations for the 3 analytes can be attributed to the fact that PK samples were taken at any time during the visit rather than at a fixed time point postdose, and therefore, the summary statistics per visit reflects the spread of PK samples at different postdose times.

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Safety results:

- There were no cases of PML identified during the study, the 12-Week Drug-Free FU Period, or by the 80-Week FU Visit.
- There were no deaths in the study. No consistent pattern was observed with serious adverse events (SAEs) with the exception of elevated liver enzymes.
- The incidence of subjects with at least 1 treatment-emergent adverse event (TEAE) was 89.7% and 96.1% in the (CDP323 500mg/day and CDP323 1000mg/day treatment groups, respectively, and 84.9% in the placebo group. Overall, in both the placebo and CDP323 treatment groups, TEAEs were reported most commonly in the Nervous system disorders, Infections and infestations, and Gastrointestinal disorders system organ class (SOCs).
- Multiple sclerosis relapse was the most commonly reported TEAE and occurred at similar rates across all treatment groups. Headache and nasopharyngitis were also commonly reported at similar rates across all treatment groups.
- Treatment-emergent AEs associated with liver function occurred at higher rates in subjects treated with CDP323 compared with placebo. Alanine aminotransferase (ALT) increased was reported for 2 subjects (2.6%) in the CDP323 500mg/day group, 7 subjects (9.1%) in the CDP323 1000mg/day group, and 1 subject (1.3%) in the placebo group. Aspartate aminotransferase (AST) increased was reported for 2 subjects (2.6%) in the CDP323 500mg/day group, 7 subjects (9.1%) in the CDP323 1000mg/day group, and zero subjects in the placebo group. Gamma-glutamyltransferase (GGT) increased was reported for 1 subject (1.3%) in the CDP323 500mg/day group, 5 subjects (6.5%) in the CDP323 1000mg/day group, and 1 subject (1.3%) in the placebo group.
- Overall, across the placebo and CDP323 treatment groups, treatment-related adverse events (AEs) were reported most commonly in the Nervous system disorders and Gastrointestinal disorders SOCs, with headache as the most commonly reported treatment-related TEAE.
- With the exception of the discontinuations due to the termination of the study, most of the discontinuations were due to AEs. One subject in the CDP323 500mg/day group and 4 subjects in the CDP323 1000mg/day group experienced AEs related to liver function that led to discontinuation.

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- No meaningful change from Baseline in median value was noted in hematology parameters with the exception of lymphocytes. Compared with placebo, based on median changes from Baseline, there were increased levels of lymphocytes at Week 28 in subjects in both the CDP323 500mg/day group (0.290×10^9/L increase) and CDP323 1000mg/day group (0.380×10^9/L increase). By Week 40, these increases had dissipated.
- No meaningful change from Baseline in median value was noted in clinical chemistry parameters with the exception of parameters associated with liver function. Compared with placebo, based on median changes from Baseline, there were increased levels of ALT, AST, and GGT at Week 28 in subjects in the CDP323 500mg/day group and the CDP323 1000mg/day group.
- A total of 13 CDP323-treated subjects had Common Terminology Criteria (CTC) Grade ≥3 results in 1 or more liver function test (LFT) parameter (ALT, AST, GGT). Seven of these subjects were able to complete the study. One subject had an elevated CTC Grade 3 ALT level prior to the initiation of study drug. All 13 cases of LFT elevations were temporary and returned to normal range eventually, after discontinuation of treatment.
- No meaningful changes from Baseline were noted in urinalysis parameters, ECG assessments, vital sign parameters, or physical examinations.
- The majority of subjects were negative for TB (96.5%) and toxoplasmosis (71.7%) at Baseline and remained negative throughout the study.

Conclusions:

- At both the interim and final analysis, CDP323 administered at either 500mg/day or 1000mg/day did not demonstrate a statistically significant difference from placebo for the primary endpoint of cumulative newly active lesions and did not provide the level of efficacy expected for an α-4 integrin inhibitor.
- The CTC Grade 3 (or higher) cases of elevated liver enzymes occurred with active treatment and appeared to be associated more with longer drug exposures rather than dose.
- With the exception of elevated LFTs, no other safety issues were observed. No cases of PML or other serious infection occurred.

Report date: 17 Dec 2010