# # 704.08 / CC68

# SAFETY AND PHARMACOKINETIC STUDY OF PHOSPHODIESTERASE 10A INHIBITOR (CPL500036) AFTER A SINGLE DOSE IN HEALTHY VOLUNTEERS

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S.J., J.S, M.M. are an employees of Celon Pharma S.A. M.M., M.W. are shareholders of Celon Pharma S.A. S.J., M.M. and M.W are patent authors..

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## INTRODUCTION

Phosphodiesterase 10A (PDE10A) hydrolyses cyclic nucleotides and is highly expressed in striatal medium spiny neurons (MSNs). PDE10A inhibition may modulate the MSNs action in an efficient way. Therefore, PDE10A inhibitors may be used in the treatment of various types of psychosis. In the course of preclinical development CPL500036 proved to be effective in several animal models of psychotic and neuromotor disorders. The present study was intended to determine the safety and pharmacokinetic properties of CPL500036 after single oral administration in healthy volunteers.

## MATERIALS AND METHODS

**Study design:**

- This was an open label, dose-escalation study with single oral administration of CPL500036 in healthy volunteers.
- The study was performed in conventional ‚3+3' design, where MTD (maximum tolerated dose) is to be determined, and decision on dose escalation is made based on dose limiting toxicities (DLT) occurence.
- The seven cohorts of subjects (n=3/ cohort) administered one dose of investigational medicinal product (IMP) with CPL500036 as an active pharmaceutical ingredient in fasted state.


Ryc.1. Dose escalation scheme.

**Study population:**

- 21 healthy subjects (18-55 years old), non-smokers, who met all the inclusion and none of the exclusion criteria were enrolled.

**Investigational Medicinal Product (IMP):**

- IMP with CPL500036 as an active pharmaceutical ingredient, as hard gelatin capsules.

**Pharmacokinetics:**

- Blood samples for PK analysis were collected in following time-points: predose (≤ 1h before the IMP administration), 15, 30, 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 10, 14, 24, 48, 72 h after IMP administration.
- CPL500036 concentration measurements were performed in human $K_3$EDTA plasma samples using HPLC/MS/MS method.

**Safety evaluation:**

- Safety assessments included: adverse events (AE) monitoring, clinical laboratory tests (haemathology, blood chemistry, urinalysis), vital signs measurements, physical examination, electrocardiography (ECG).

**Statistics:**

- Demographic data was analysed descriptively.
- PK parameters were derived individually for each subject and computed using a non-compartmental modelling approach. PK parameters were analysed with descriptive summary statistics (incl. mean and standard deviation). Time-course plasma concentration profile of all subjects and mean for each cohort were determined.
- Adverse events were evaluated descriptively.

## RESULTS

### DEMOGRAPHICS

Tab.1. Demographic data by sex.

| | Age [years] | Height [cm] | Weight [kg] | BMI [kg/m²] |
|---|---|---|---|---|
| Males | | | | |
| N | 13 | 13 | 13 | 13 |
| Mean | 36.5 | 180.4 | 79.8 | 24.4 |
| SD | 8.0 | 9.6 | 14.2 | 2.5 |
| Min | 26.0 | 161.0 | 51.0 | 19.7 |
| Max | 52.0 | 200.0 | 111.1 | 27.8 |
| Females | | | | |
| N | 8 | 8 | 8 | 8 |
| Mean | 36.8 | 167.8 | 62.8 | 22.3 |
| SD | 8.5 | 3.5 | 5.7 | 2.0 |
| Min | 22.0 | 163.0 | 53.5 | 19.2 |
| Max | 47.0 | 175.0 | 70.0 | 25.4 |

### ADVERSE EVENTS - DETAILES

Tab.2. Adverse events observed during the study.

not related

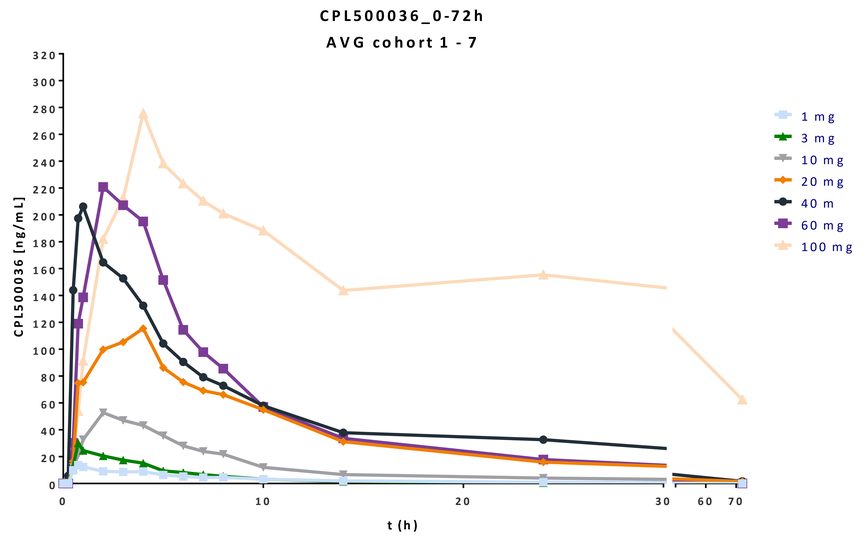
| AE | CPL500036 Dose | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 mg | 3 mg | 10 mg | 20 mg | 40 mg | 60 mg | 100 mg |
| ANXIETY | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | **3 (50.0 %)** |
| COLD | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (50.0 %) | 2 (28.6 %) | 0 (0.0 %) | 0 (0.0 %) |
| COLLAPSING | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (50.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
| COUGH | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (14.3 %) | 0 (0.0 %) | 0 (0.0 %) |
| DECREASE OF GLUCOSE LEVEL IN BLOOD | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (14.3 %) | 0 (0.0 %) | 0 (0.0 %) |
| DIFFICULTY SPEAKING | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | **1 (14.3 %)** | 0 (0.0 %) | 0 (0.0 %) |
| DROWSINESS | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | **2 (50.0 %)** | **2 (33.3 %)** |
| ELEVATED BILIRUBIN IN BLOOD | 0 (0.0 %) | 0 (0.0 %) | 1 (100.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
| HEADACHE | 1 (100.0) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |
| HERPES | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (14.3 %) | 0 (0.0 %) | 0 (0.0 %) |
| SENSATION OF HEAT | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | **1 (14.3 %)** | **2 (50.0 %)** | 0 (0.0 %) |
| SHAKING INTENT | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | **1 (16.7 %)** |
| SOFT FEACES | 0 (0.0 %) | 1 (100.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) |

### ADVERSE EVENTS - TOTAL

Tab.3. Total number of AEs by dose, intensity and relationship to the study IMP.

| Total | | N = 22 | |
|---|---|---|---|
| Dose | 1mg | 1 | 4,55% |
| | 3mg | 1 | 4,55% |
| | 10mg | 1 | 4,55% |
| | 20mg | 2 | 9,09% |
| | 40mg | 7 | 31,82% |
| | 60mg | 4 | 18,12% |
| | 100mg | 6 | 27,27% |
| Intensity | Mild | 9 | 40,91% |
| | Moderate | 13 | 59,09% |
| | Severe | 0 | 0% |
| Relationship to the study IMP | Not related | 10 | 45,45% |
| | Possible related | 10 | 45,45% |
| | Related | 2 | 9,1% |

### PHARMACOKINETICS




Ryc.2. Mean of CPL500036 plasma concentration.

Tab.4. CPL500036 pharmacokinetic parameters [mean, (SD)].

| | Cohort | N | $C_{max}$ [ng/mL] | $T_{max}$ [h] | $T_{1/2}$ [h] | $AUC_{(0\text{-}24h)}$ [ng/mL*h] | $AUC_{(0\text{-}72h)}$ [ng/mL*h] |
|---|---|---|---|---|---|---|---|
| CPL500036 | 1 | 3 | 13.757 (5.633) | 0.833 (0.144) | 6.021 (4.223) | 91.410 (70.190) | 105.854 (87.781) |
| | 2 | 3 | 30.147 (11.298) | 0.750 (0.000) | 4.156 (0.180) | 134.315 (115.028) | 134.315 (115.028) |
| | 3 | 3 | 54.507 (35.546) | 1.500 (0.866) | 5.291 (1.549) | 394.990 (368.040) | 446.311 (445.753) |
| | 4 | 3 | 133.098 (50.786) | 2.917 (1.876) | 10.645 (3.848) | 1183.013 (873.113) | 1474.941 (1154.166) |
| | 5 | 3 | 213.614 (50.182) | 1.250 (0.661) | 7.071 (4.089) | 1650.756 (1370.019) | 2170.120 (2243.032) |
| | 6 | 3 | 226.905 (67.158) | 2.333 (0.5777) | 6.220 (2.700) | 1735.405 (315.713) | 1870.958 (203.458) |
| | 7 | 3 | 284.955 (239.324) | 3.000 (1.732) | 24.560 (20.531) | 4067.963 (3626.694) | 9493.894 (8305.182) |

## SUMMARY AND CONCLUSIONS

- CPL500036 was generally safe and well tolerated without serious AEs at all doses up to 100mg.
- No dose limiting toxicity (DLT) was observed at any dose, therefore no maximum tolerated dose (MTD) was determined.
- Most reported adverse events were classified as mild to moderate severity.
- Most frequent reported AEs related or possibly related to IMP were anxiety, drowsiness, sensation of heat and difficulty speaking.
- CPL500036 exposure increased in the dose-dependent manner.
- The study results justify further clinical development of CPL500036 compound.

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