5026

SAFETY ASSESSMENT OF CPL'36 (PDE10A INHIBITOR) IN PATIENTS WITH ACUTE EXACERBATION OF SCHIZOPHRENIA – results from a phase 2 trial

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Disclosures:
J.S-P., M.M., P.J.R., R.J. are an employees of Celon Pharma S.A. M.M., P.J.R. and M.W. are shareholders of Celon Pharma S.A. M.M. and M.W are patent authors.

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INTRODUCTION

Phosphodiesterase 10A (PDE10A) is a member of the phosphodiesterase family that hydrolyzes cAMP and cGMP, and is highly expressed in striatal medium spiny neurons (MSNs). Inhibition of PDE10A can modulate MSN activity and has potential as a treatment for various forms of psychosis. We have developed **a second-generation PDE10A inhibitor, CPL'36 (CPL500036), with improved pharmacodynamic characteristics**. Its unique profile, featuring rapid dissociation from the enzyme, ensures high efficacy as confirmed by nonclinical assessments. In a Phase I clinical study, CPL'36 exhibited good tolerability, safety and linear pharmacokinetics. Here, we present the safety results from a 28-day administration of CPL'36 in the treatment of acute exacerbation of schizophrenia.

MATERIALS AND METHODS

Study design:

- This was a randomized, double-blind, placebo controlled, parallel-group, multicentre phase II study to Explore Efficacy, Safety and PK of CPL'36 in patients with acute exacerbation of schizophrenia.

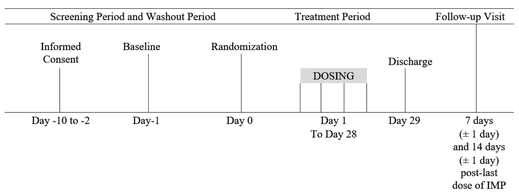


Fig.1. Trial Design

- 189 patients were randomized in 1:1:1 ratio to three therapeutic arms: 20 or 40 mg of CPL'36 or placebo.
- CPL'36 was administered orally, once daily, morning for 28 consecutive days.

Study population:

- Male or female aged 18 to 65, inclusive, with primary diagnosis of schizophrenia (as per DSM-5 criteria) with exacerbation of psychotic symptoms within 2 months prior screening and total score in Positive and Negative Syndrome Scale (PANSS) greater than or equal to 80.
- Patients remained off other antipsychotics medication during treatment period.

Investigational Medicinal Product (IMP):

- CPL500036 was administered in a form of powder in a hard gelatin capsule. Each capsule contained 10 mg of active substance and excipients.
- Placebo capsule matching CPL'36 capsule and contained only mannitol.

Safety evaluation:

- Safety assessment included: adverse events (AE) reporting, clinical laboratory tests, vital signs, electrocardiography (ECG), physical, neurological, ophthalmological and dermatological examination and extrapyramidal symptom by ESRS (Extrapyramidal Symptom Rating Scale).

Statistics:

- Demographic data was analyzed descriptively.
- The number and percentage of patients reporting the AE and the number of AEs reported was determined. Comparison of pre-dose and post-dose values for clinical laboratory data, vital signs and ECG were assessed.
- For ESRS results descriptive statistics of the total score and changes from baseline were calculated.

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Tab.1. Demographic and baseline characteristics [mean, SD]

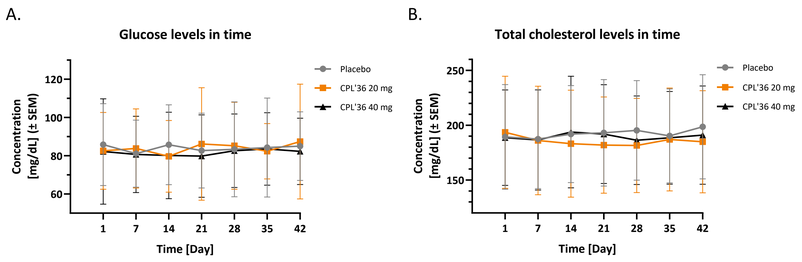
Category		Placebo, N=65	CPL'36 20 mg, N=58	CPL'36 40 mg, N=66
Age [years], mean (SD)		41.5 (10.6)	41.3 (9.8)	42.1 (10.0)
Sex, n (%)	Male	46 (70.8%)	32 (55.2%)	41 (62.1%)
	Female	19 (29.2%)	26 (44.8%)	25 (37.9%)
Race, n (%)	Caucasian*	65 (100.0%)	58 (100.0%)	66 (100.0%)
Duration of disease, mean (SD), years		14.9 (9.2)	14.2 (8.9)	15.7 (9.6)
PANSS total score, mean (SD)		103.4 (10.8)	106.4 (9.9)	106.5 (11.4)

*In the source data race was defiined as Caucasian and Other (White).

METABOLIC PROFILE

Glucose and total cholesterol levels remained constant in patients plasma throughout the study.

Fig.2. Glucose levels (A) and total cholesterol levels (B) in patients plasma during the study



During treatment phase samples were collected pre-dose (≤ 1h before IMP administration).

ADVERSE EVENTS

Tab.2. Summary of patients with at least one adverse events [number of patients (%)], Safety Set

Category	Placebo, N=65	CPL'36 20 mg, N=57	CPL'36 40 mg, N=65
Treatment emergent AE (TEAE)	22 (33.8%)	25 (50.9%)	37 (56.9%)
Treatment emergent SAE (TESAE)	1 (1.5%)	1 (1.8%)	2 (3.1%)
Severe TEAE	2 (3.1%)	5 (8.8%)	3 (4.6%)
Related severe TEAE	1 (1.5%)	4 (7.0%)	2 (3.1%)
Related TEAEs leading to permanent discontinuation of study medication	2 (3.1%)	1 (1.8%)	5 (7.7%)
Specific adverse events with incidence >5% in any treatment group			
Somnolence	**0 (0.0%)**	**9 (15.8%)**	**8 (12.3%)**
Drug related	0 (0.0%)	9 (15.8%)	7 (10.8%)
Anxiety	**6 (9.2%)**	**6 (10.5%)**	**9 (13.8%)**
Drug related	4 (6.2%)	1 (1.8%)	4 (6.2%)
Insomnia	**5 (7.7%)**	**4 (7.0%)**	**5 (7.7%)**
Drug related	0 (0.0%)	0 (0.0%)	2 (3.1%)
Schizophrenia (worsening of symptoms)	**2 (3.1%)**	**4 (7.0%)**	**7 (10.8%)**
Drug related	1 (1.5%)	1 (1.8%)	3 (4.6%)
EPS*	**0 (0.0%)**	**5 (8.8%)**	**8 (12.3%)**
Drug related	0 (0.0%)	4 (7.0%)	7 (10.8%)

*EPS (extrapyramidal symptoms) includes akathisia, extrapyramidal disorder, dystonia, tremor and psychomotor hyperactivity.

HEPATIC PARAMETERS

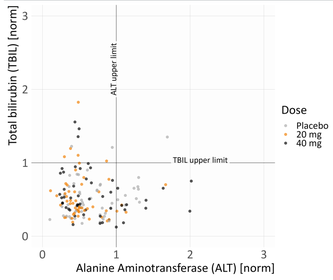
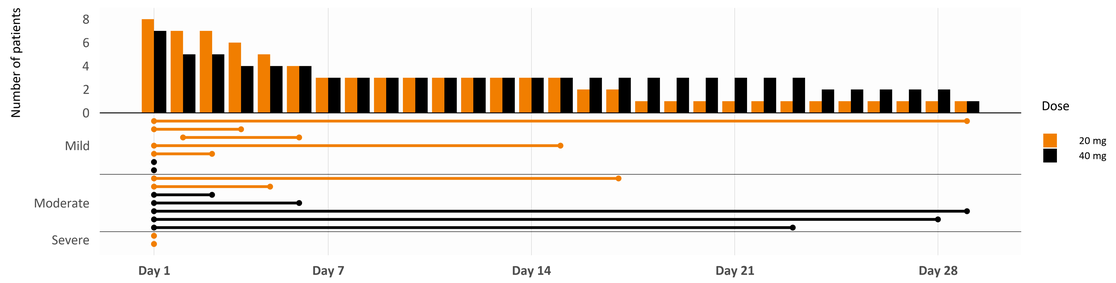


Fig. 3. Assessment of Total Bilirubin (TBIL) and Alanine Aminotransferase (ALT) according to the upper normal range as multiple of the norm

ADVERSE EVENTS DETAILS - SOMNOLENCE

Fig.4. Distribution of somnolence over time



SUMMARY AND CONCLUSIONS

- CPL'36 is a second-generation PDE10A inhibitor with unique profile, featuring rapid dissociation from the enzyme.
- CPL'36 demonstrated a favorable safety and tolerability profile in both tested doses.
- Most frequent reported AEs observed in all arms were somnolence, anxiety, insomnia and worsening of schizophrenia symptoms with intensity from mild to moderate.
- CPL'36 did not cause clinically significant increased the tested metabolic parameters (glucose and total cholesterol levels) and hepatic parameters during the study.
- The study results justify further clinical development of CPL'36 compound.

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