



# PDE10A Inhibition in Schizophrenia: A Randomised, Placebo-Controlled Phase 2 Study of Alofropodect (CPL'36) in Patients Experiencing Acute Schizophrenia

Maciej Wieczorek<sup>1</sup> · Napoleon Waszkiewicz<sup>2</sup> · Ewa Gromniak-Haniecka<sup>3</sup> · János M. Réthelyi<sup>4</sup> · Mykhaylo Pustovoyt<sup>5</sup> · Yuriy Filts<sup>6</sup> · Yuliya Blazhevych<sup>7</sup> · Mikołaj Matłoka<sup>1</sup> · Sylwia Janowska<sup>1</sup> · Barbara Łapińska<sup>1</sup> · Piotr J. Rudzki<sup>1</sup> · Radosław Jaźwiec<sup>1</sup> · Joanna Sierzputowska-Prarat<sup>1</sup>

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## Abstract

**Background** Drugs that inhibit phosphodiesterase 10A (PDE10A) activity have shown efficacy in animal models. However, clinical trials of PDE10A inhibitors in patients with schizophrenia have failed to provide clinically significant results up to this point. Our study investigated whether alofropodect (previously referred to as CPL'36 or CPL500036), a PDE10A inhibitor with an improved pharmacological profile compared with other PDE10A inhibitors, including a fast dissociation rate and high activity, could improve symptoms of acute schizophrenia.

**Methods** In this phase 2, randomised, double-blind, placebo-controlled, parallel-group trial (11 centres, three countries), investigators randomly assigned hospitalised patients with acute schizophrenia to treatment or placebo groups. The main inclusion criteria were age 18–65 years, a documented diagnosis of schizophrenia for at least 2 years before screening and a positive and negative syndrome scale (PANSS) total score  $\geq 80$ . Participants were randomly assigned (1:1:1) to receive oral alofropodect (20 mg or 40 mg) or placebo administered once daily in the morning for 4 weeks. The primary endpoint of the study was an improvement in the PANSS positive subscale at week 4. The secondary endpoints included improvements in PANSS total and negative subscale scores, along with other efficacy and safety assessments. Clinical responders were defined as those with a  $\geq 30\%$  reduction in PANSS total score from baseline at week 4.

**Results** Between 24 May 2021 and 8 May 2024, investigators randomised 189 patients into three groups: 58 into the alofropodect 20 mg group, 66 into the alofropodect 40 mg group and 65 into the placebo group. The mean age was 41.7 years (standard deviation (SD) 10.1), and 119 (63%) participants were men, 70 (37%) were women. All participants were White. We measured the difference in PANSS positive subscale before and after treatment, and the change met the primary endpoints at week 4 with the group where alofropodect 20 mg was compared with placebo ( $-3.70$  [90% CI  $-5.51$  to  $-1.89$ ];  $p < 0.001$ ) and alofropodect 40 mg versus placebo ( $-6.35$  [90% CI  $-8.12$  to  $-4.57$ ];  $p = 0.001$ ). Both the 20-mg and 40-mg doses of alofropodect were effective in improving the total PANSS score compared with placebo and met most secondary efficacy endpoints. A clinical response was observed in 2 of 53 patients (3.8%) in the placebo group, 8 of 52 patients (15.4%) in the 20 mg group and 22 of 52 patients (42.3%) in the 40 mg group at week 4. The compound was well tolerated, with only a few serious adverse events. The discontinuation rates were similar in the placebo and treatment arms. Extrapyramidal symptoms (EPS) occurred only in the active treatment groups, but rates were low overall. Somnolence was also reported only in alofropodect groups. Vital signs and biochemical parameters remained unaffected by either dose at any time point. Specifically, blood glucose, total cholesterol and triglycerides did not increase at any dose compared with placebo within our study window.

**Conclusions** Alofropodect was effective in the treatment of acute schizophrenia symptoms and was well-tolerated, warranting further investigation in larger clinical studies.

**Clinical Trial Registration** Clinicaltrials.gov identifier: NCT05278156; registration date: 2022-02-09.

## Key Points

Alofropodect is a novel, second-generation PDE10A inhibitor with an improved clinical outcome compared with others in its class.

In this phase 2, randomised, double-blind, placebo-controlled trial, 189 hospitalised patients with acute schizophrenia were administered alofropodect (20 mg or 40 mg) or placebo for 4 weeks.

Alofropodect significantly attenuated symptoms associated with schizophrenia and was well-tolerated, with no adverse biochemical changes, supporting further investigation in larger studies.

## 1 Introduction

Schizophrenia has imperfect pharmacological management that includes problems related to insufficient efficacy and tolerability. Approximately 20–30% of patients show no response, while an additional 30% demonstrate only partial response to treatment [1]. Moreover, first-generation antipsychotics, owing to their strong blockade of D2 receptors, frequently cause adverse effects such as extrapyramidal symptoms (e.g., catalepsy) and hyperprolactinemia [2]. Second-generation antipsychotics were developed largely in response to the need to reduce these side effects and although they are associated with a lower incidence of extrapyramidal symptoms, their use is often linked to the development of metabolic syndrome, including diabetes, obesity and dyslipidaemia [3]. For both classes of drugs, adverse effects on the cardiovascular system have been observed, including QT interval prolongation on electrocardiography, which may lead to life-threatening cardiac arrhythmias [4]. Selected antipsychotics may also cause leukopenia or agranulocytosis. Drug resistance and adverse effects result in poor treatment adherence in up to 50% of patients [5].

Furthermore, currently available therapies primarily target the positive symptoms of schizophrenia, with little or no effect on negative and cognitive symptoms, which are the main factors limiting patients' ability to function independently [6]. This strong unmet need drives research into novel drug targets.

Biochemical and behavioural data suggest that phosphodiesterase 10A (PDE10A) inhibition modulates cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) signalling in the basal ganglia, suppressing D2 receptor

activity and potentiating D1 receptor activity [7, 8]. Notably, PDE10A is an enzyme almost exclusively expressed in the striatum, making it a viable therapeutic target for schizophrenia [9]. Although several preclinical experiments have validated PDE10A inhibition in multiple animal models of psychosis, including conditioned avoidance response, amphetamine-induced locomotion and phencyclidine-disrupted pre-pulse inhibition [10], PDE10A inhibitors have shown mixed results in clinical trials thus far. Several compounds, including PF-02545920 (mardepodect, MP-10) and Lu AF11167 failed to demonstrate efficacy in phase 2 trials for schizophrenia [11–12].

Out of the group of known PDE10A inhibitors, two have shown signals of antipsychotic activity. The first, TAK-063 (balipodect), was tested at a single 20 mg dose in a 6-week placebo-controlled trial ( $N = 164$ ), but did not meet its primary endpoint of improvement on the PANSS total score, and demonstrated significant improvement on the clinical global impression–improvement scale ( $p = 0.007$ , effect size 0.53) [13, 14]. The second, MK-8189 (elpipodect), a controlled-release PDE10A inhibitor achieving over 60% enzyme occupancy, showed a trend towards improvement in the PANSS total score and a nominally significant improvement in the PANSS positive subscale in a proof-of-concept trial ( $N = 224$ ). Assay sensitivity was confirmed by the risperidone active comparator arm ( $p = 0.033$  versus placebo) [15]. However, a phase 2b clinical study on MK-8189 did not replicate the positive results of the previous trial [16]. Together, these results suggest that PDE10A is a viable but pharmacologically demanding target: one where the magnitude and pattern of enzyme inhibition, the choice of dose and the quality of trial execution may all influence the likelihood of detecting a clinical signal.

Celon Pharma S.A. has developed alofropodect (previously known as CPL'36 and CPL500036) [17, 18], a second-generation PDE10A inhibitor with an improved pharmacological profile. Its molecular features, together with pharmacokinetics supporting once-daily dosing and a favourable safety profile in healthy volunteers, provided the rationale for the present phase 2 study.

This trial aimed to assess the efficacy, safety and tolerability of two fixed doses of alofropodect (20 mg and 40 mg once daily), compared with placebo, in adults experiencing an acute exacerbation of schizophrenia.

## 2 Methods

### 2.1 Participants

Eligible patients were 18–65 years old, had a Diagnostic and Statistical Manual of Mental Disorders 5th Edition

(DSM-V) diagnosis of schizophrenia confirmed by the mini international neuropsychiatric interview (MINI) for schizophrenia and psychotic disorders studies, experienced an acute exacerbation and scored  $\geq 4$  on the clinical global impression scale-severity of illness scale (CGI-S). We defined an acute exacerbation as the occurrence of a PANSS total score  $\geq 80$  during screening and on day - 1, and a score  $\geq 5$  (moderate-severe) in 3 or more of the following PANSS items at screening and day - 1: delusions (P1), conceptual disorganisation (P2), hallucinations (P3), suspiciousness (P6) and unusual thought content (G9).

All patients were hospitalised for the duration of the treatment period. All were required to be non-pregnant and to use a protocol-defined effective method of contraception. Patients were excluded if they had a decrease in the PANSS total score by 20% or more at baseline (day - 1) compared with the screening or had treatment-resistant schizophrenia (defined as a prior non-response to two courses of treatment with antipsychotics of different chemical classes for at least 4 weeks each). After obtaining written informed consent from all patients, we initiated any study-related procedures. The full inclusion and exclusion criteria are available in the study protocol [19].

## 2.2 Study Design

Our study was a phase 2, randomised, double-blind, dose-ranging, placebo-controlled, parallel-group study evaluating the efficacy, safety and pharmacokinetics (PK) of alofropodect in patients with acute schizophrenia [19]. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. An institutional review board and an independent ethics committee approved the protocol and the patients' informed consent before study initiation.

After screening, eligible patients were randomly assigned 1:1:1 to receive 20 mg, 40 mg, or a placebo (Supplementary Appendix 2). The study lasted approximately 8 weeks: screening ( $\leq 10$  days), treatment (4 weeks), follow-up (2 weeks). We utilised a rolling admission process. If needed, patients underwent a medication washout period ( $\leq 7$  days) in the clinical unit before randomisation. During in-house treatment (days 1–28), patients received 20 mg, 40 mg, or a placebo.

Approximately 30% of participants (17 per treatment group) underwent extensive PK sampling during the treatment period, while the remaining participants underwent sparse sampling. Alofropodect concentrations in plasma were measured using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with an isotope-labelled internal standard.

On day 29, participants could resume standard-of-care antipsychotic treatment. The investigator(s) continued to monitor the participant for safety and clinical stability after the treatment period had ended. Patients were discharged from the clinical unit on the basis of the local standard-of-care if they were in a stable condition with their regular psychiatric medication(s). After discharge from the clinical unit, participants were asked to return for two once-weekly follow-up visits,  $7 \pm 1$  and  $14 \pm 1$  days after the last dose. Participants who withdrew from the study, or were withdrawn, could attend an early termination visit at the clinical unit and two safety follow-up visits,  $7 \pm 1$  and  $14 \pm 1$  days after the last dose.

## 2.3 Outcomes

The primary endpoint was a change from baseline (CfB) in the PANSS positive subscale score at week 4. Secondary endpoints at weeks 1, 2 and 3 included a CfB in the PANSS positive subscale [20]. In weeks 1–4, they included CfB in the PANSS total score, PANSS negative subscales, PANSS subscales using the Marder 5-factor model (M5M), PANSS general psychopathology subscale, clinical global impression-severity (CGI-S) score and the clinical global impression-improvement scale (CGI-I) score. At weeks 2 and 4, they included a change in the brief assessment of cognition in schizophrenia (BACS) score. We measured participant responses as the 'response rate' on the PANSS total score, with a clinical responder defined as a decrease in symptoms of  $\geq 30\%$  from baseline. The CGI-I rating score for 'response rate' was defined as the ratings 'much improved' or 'very much improved.'

We used the extrapyramidal symptom rating scale (ESRS) to assess four types of drug-induced movement disorders (DIMS): parkinsonism, akathisia, dystonia and tardive dyskinesia. These disorders were evaluated at screening, baseline, on day 1 during treatment, at weeks 1, 2, 3 and 4 and during follow-up (weeks 5 and 6).

Discontinuations from, incidence to and the severity of adverse events (AEs), serious AEs (SAEs) and treatment-emergent adverse events (TEAEs) were examined and classified by system organ class and preferred term.

The pharmacokinetics of alofropodect in plasma were evaluated in extensive and sparse groups. The alofropodect concentration and PK parameters were summarised using descriptive statistics, stratified by sampling group (Supplementary Appendix 3).

## 2.4 Statistical Analysis

In this proof-of-concept study, the sample size was calculated to ensure sufficient power to rule out a clinically meaningful

effect size of 0.5 or greater for the primary endpoint. With 50 participants per group, the study had 80% power to detect an effect size of 0.5 or greater for one of the two dose groups compared with placebo, given a two-sample *t* test and a two-sided 10% significance level. The study initially assumed a 10% dropout rate with a target of 165 participants reaching day 28.

The full analysis set (FAS) of participants was the primary analysis set used for all efficacy analyses, and the per protocol (PP) analysis set was used for supportive analyses of the primary and secondary efficacy endpoints [20]. Missing data were assumed to be missing at random. The safety analysis set was used for all safety analyses, and participants were included in the treatment group on the basis of the treatment they received.

For the primary efficacy analysis, a Cfb in the PANSS positive subscale score (up to week 4 of the treatment phase) was analysed using a mixed model for repeated measures (MMRM), accounting for treatment (20 mg, 40 mg), time point, the interaction between treatment and time point, clinical site and the baseline score as a continuous covariate. We treated subjects as random effects, with an unstructured covariance structure to account for correlations among repeated measurements. Our null hypothesis was that there would be no differences in the primary endpoint between the treatment group and placebo at week 4. Our alternative hypothesis was that at least one treatment group would exhibit a clinically significant effect compared with placebo. The alternative hypothesis was tested at a 10% two-sided significance level. There were no multiplicity adjustments for comparisons of each dose of alogliptin versus placebo at week 4. The continuous secondary endpoints were analysed using the same approach as described for the primary endpoint using MMRM (Supplementary Appendix 4).

The percentage of participants in each AEs category was compared between treatments using a difference-in-proportions test, with 95% CIs based on the Agresti–Caffo method [21]. TEAEs were analysed on the basis of their relationship to the study medication, documented as ‘unlikely,’ ‘possible,’ ‘probable’ or ‘definite,’ or as missing.

## 3 Results

### 3.1 Study Participants

Between 24 May 2021 and 8 May 2024, 207 patients across three countries (Poland, Hungary and Ukraine) and 11 clinical sites were assessed for eligibility (Table 1, Fig. 1). Of these, 18 patients were excluded and 189 patients were randomised, with 157 (76%) completing the treatment period of the study. Patients who finished within each group: placebo group, 53 of 65 (82%); 20 mg group, 52 of 58 (90%) and 40

mg group, 52 of 66 (79%). Across treatment groups, baseline demographic and disease characteristics were generally well balanced (Table 1). All patients who completed the clinical trial had previously received antipsychotic treatment. Therefore, statistical analysis of the clinical responses of pretreated versus non-treated patients was not performed.

### 3.2 Efficacy (Primary Endpoint)

#### 3.2.1 PANSS Positive at Week 4

Both treatment doses showed statistically significant improvements in the primary endpoint (Cfb PANSS positive at week 4). For the 20 mg dose, the least squares (LS) mean difference was  $-3.70$  (90% CI  $-5.51$  to  $-1.89$ ; nominal  $p < 0.001$ ). For the 40 mg dose, the LS mean difference was  $-6.35$  (90% CI  $-8.12$  to  $-4.57$ ; nominal  $p < 0.001$ ) (Fig. 2). The corresponding absolute LS mean Cfb in PANSS positive was  $-4.90$  (90% CI  $-6.20$  to  $-3.60$ ) for the 20 mg dose and  $-7.55$  (90% CI  $-8.80$  to  $-6.29$ ) for the 40 mg dose.

### 3.3 Efficacy (Secondary Endpoints)

#### 3.3.1 PANSS Total, Positive, Negative

Cfb PANSS total score at week 4 for both 20 mg and 40 mg showed a statistically significant difference from placebo (Fig. 2, Supplementary Table 1). For 20 mg, the LS mean difference was  $-9.68$  (90% CI,  $-14.03$  to  $-5.32$ ;  $p < 0.001$ ). For the 40 mg dose, the LS mean difference was  $-16.40$  (90% CI,  $-20.69$  to  $-12.11$ ;  $p < 0.001$ ). A statistically significant improvement over placebo was observed in the Cfb PANSS total score from week 1 onward and continued throughout the study.

Cfb PANSS positive subscale at weeks 1, 2 and 3 showed statistically significant improvement versus placebo for both doses (Fig. 2).

The Cfb PANSS negative subscale scores improved significantly versus placebo at weeks 2 and 3 in both doses and at week 4 in the 40 mg dose, achieving a LS mean difference from placebo of  $-2.56$  (90% CI  $-3.51$  to  $-1.62$ ;  $p < 0.001$ ). The 20 mg dose marginally missed statistical significance at week 4 ( $p = 0.083$ ) (Fig. 2).

Scores for Cfb PANSS general psychopathology showed statistically significant improvement from placebo at all time points in the 20 mg dose and, starting from week 2, in the 40 mg dose. At the end of week 4, the LS mean difference in the 20 mg dose was  $-4.56$  (90% CI  $-6.88$  to  $-2.25$ ;  $p = 0.001$ ). For the 40 mg dose, the LS

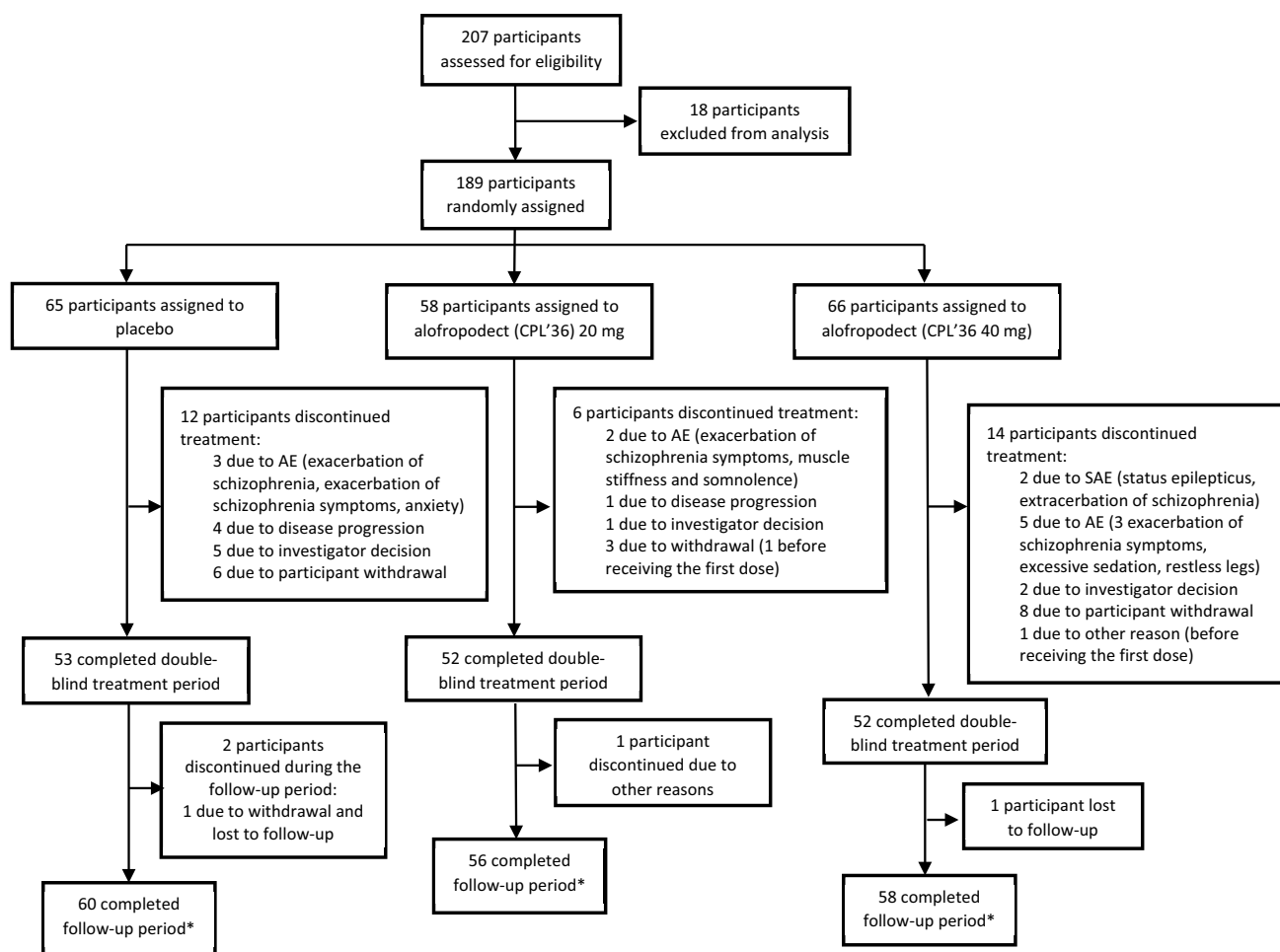


**Fig. 1** Trial profile flow diagram showing 207 participants assessed for eligibility, with 189 randomised to placebo or alofropoect doses and follow-up completion rates. Investigators could have provided more than one reason for discontinuation. 'Due to investigator deci-

sion' means that in the investigator's opinion, continued participation in the study was clearly disadvantageous for the patient. \*Including early-terminated patients who attended follow-up visits (day 35 and day 42). *AE* adverse event, *SAE* serious adverse event

mean difference was  $-7.59$  (90% CI  $-9.87$  to  $-5.31$ ;  $p < 0.001$ ).

Clinical response ( $\geq 30\%$  reduction in Cfb PANSS total score from baseline) at week 4 was demonstrated in 2 of 53 participants (3.8%) in the placebo group, 8 of 52 participants (15.4%) in the 20 mg dose and 22 of 52 participants (42.3%) in the 40 mg dose.

### 3.3.2 Marder 5-Factor Model (M5M), CGI-S, CGI-I, BACS

The M5M assessment showed a response pattern similar to the PANSS scores, with the 40 mg dose showing slightly greater efficacy than the 20 mg dose. The Cfb in the CGI-S score improved significantly in both doses from week 1 through the end of the study. The clinical response, as measured by CGI-I ratings, was significantly improved at both doses from week 2 through the end of the study. At week 4,

3 of 53 participants (5.7%) in the placebo group, 13 of 52 participants (25.0%) in the 20 mg group and 28 of 52 participants (53.8%) in the 40 mg group qualified as responders. The Cfb in the brief assessment of cognition in schizophrenia (BACS) showed a numerical improvement over placebo, although the difference from placebo did not reach statistical significance at week 4 (Supplementary Appendix 5, Supplementary Table 1).

## 3.4 Safety (Secondary Endpoints)

### 3.4.1 Adverse Events

The overall incidence of AEs was higher in both treatment groups compared with placebo (Table 2, Supplementary Table 2). The rate of SAEs was low across all groups, with only 2.7% of participants reporting them. Worsening of

**Table 1** Demographic and clinical baseline characteristics of participants

| Characteristic                          | Placebo<br>( <i>N</i> = 65)<br><i>N</i> (%) | Alofropodect 20 mg<br>( <i>N</i> = 58)<br><i>N</i> (%) | Alofropodect 40 mg<br>( <i>N</i> = 66)<br><i>N</i> (%) |
|-----------------------------------------|---------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Sex                                     |                                             |                                                        |                                                        |
| Male                                    | 46 (71%)                                    | 32 (55%)                                               | 41 (62%)                                               |
| Female                                  | 19 (29%)                                    | 26 (45%)                                               | 25 (38%)                                               |
| Race                                    |                                             |                                                        |                                                        |
| White                                   | 65 (100%)                                   | 58 (100%)                                              | 66 (100%)                                              |
|                                         | Mean (SD)                                   | Mean (SD)                                              | Mean (SD)                                              |
| Age (years)                             | 41 (11)                                     | 41 (10)                                                | 42 (10)                                                |
| Weight (kg)                             | 77.3 (14.0)                                 | 76.0 (17.8)                                            | 80.4 (20.7)                                            |
| BMI (kg/m <sup>2</sup> )                | 25.8 (4.4)                                  | 25.9 (6.0)                                             | 26.9 (6.2)                                             |
| Duration of disease (years)             | 14 (9)                                      | 14 (9)                                                 | 15 (10)                                                |
| Duration of current exacerbation (days) | 34 (19)                                     | 32 (18)                                                | 33 (19)                                                |
| PANSS positive score                    | 28 (3.2)                                    | 28 (3.9)                                               | 29 (3.6)                                               |
| PANSS total score                       | 103 (10.8)                                  | 106 (10.0)                                             | 107 (11.4)                                             |
| PANSS negative score                    | 26 (4.3)                                    | 27 (4.2)                                               | 27 (4.1)                                               |
| CGI-S score                             | 5 (0.5)                                     | 5 (0.5)                                                | 5 (0.5)                                                |
| BACS T-score                            | 28 (14.5)                                   | 24 (11.8)                                              | 29 (10.2)                                              |

BACS brief assessment of cognition in schizophrenia, BMI body mass index, CGI-S clinical global impression-severity scale, *N* number of patients, PANSS positive and negative syndrome scale, SD standard deviation

schizophrenia as an SAE was reported in one participant in both active groups. Possibly related to the study drug, status epilepticus occurred in one participant in the 40 mg group, which resolved.

TEAEs were reported in 47.1% of participants overall, with the highest incidence observed in the 40 mg group. The incidence of severe TEAEs was relatively low in all groups. Only one participant in the overall study population experienced a dose interruption owing to TEAE, and no participants required a dose reduction. However, 12 participants (6.4%) in the overall study population discontinued the study medication owing to TEAEs. No deaths were reported.

Most AEs were mild-to-moderate. TEAEs that were more frequent in the active treatment arms included nervous system disorders (as expected owing to alofropodect's physiological target): 3.1% in the placebo group, 26.3% in the 20 mg group and 24.6% in the 40 mg group. One case of psychomotor hyperactivity, two cases of tremor and two cases of akathisia were reported in the 20 mg dose. By contrast, participants in the 40 mg group reported one case of tremor, two cases of dystonia, two cases of psychomotor hyperactivity and three extrapyramidal disorders. All EPS cases were mild-to-moderate in intensity. The majority of cases of somnolence occurred within the first days of treatment and disappeared. Somnolence was mild-to-moderate in intensity except for two cases in the 20 mg group.

### 3.4.2 Vital Signs, Electrocardiograms, Clinical Laboratory Evaluations, Physical Examinations

No changes in vital signs, including blood pressure, were recorded at any dose or time point. ECG readings were normal throughout the study. Metabolic parameters, including blood glucose, cholesterol and triglycerides, were not increased at any dose compared with placebo (Supplementary Fig. 1). Hepatic enzyme levels remained stable throughout the treatment for all doses and they did not differ significantly from those in the placebo group (Supplementary Fig. 1). The majority of participants across all groups had no abnormal findings in the physical, neurological, ophthalmological or dermatological examinations that would affect the validity of the study's outcomes.

### 3.5 Pharmacokinetics (Secondary Endpoints)

Expected dose-dependent trends were observed through drug exposure - i.e. maximum concentration ( $C_{\max}$ ), area under the curve (AUC) - but a less-than-dose-proportional increase in exposure may be expected in future studies (Supplementary Fig. 2, Supplementary Table 3). The median time to  $C_{\max}$  ( $t_{\max}$ ) across all doses and days combined was 1.5–3.0 h (range, 0.5–8 h, except for one result at 23.5 h). No dose- or relevant time-dependent trends were observed for  $t_{\max}$ . Mean half-life

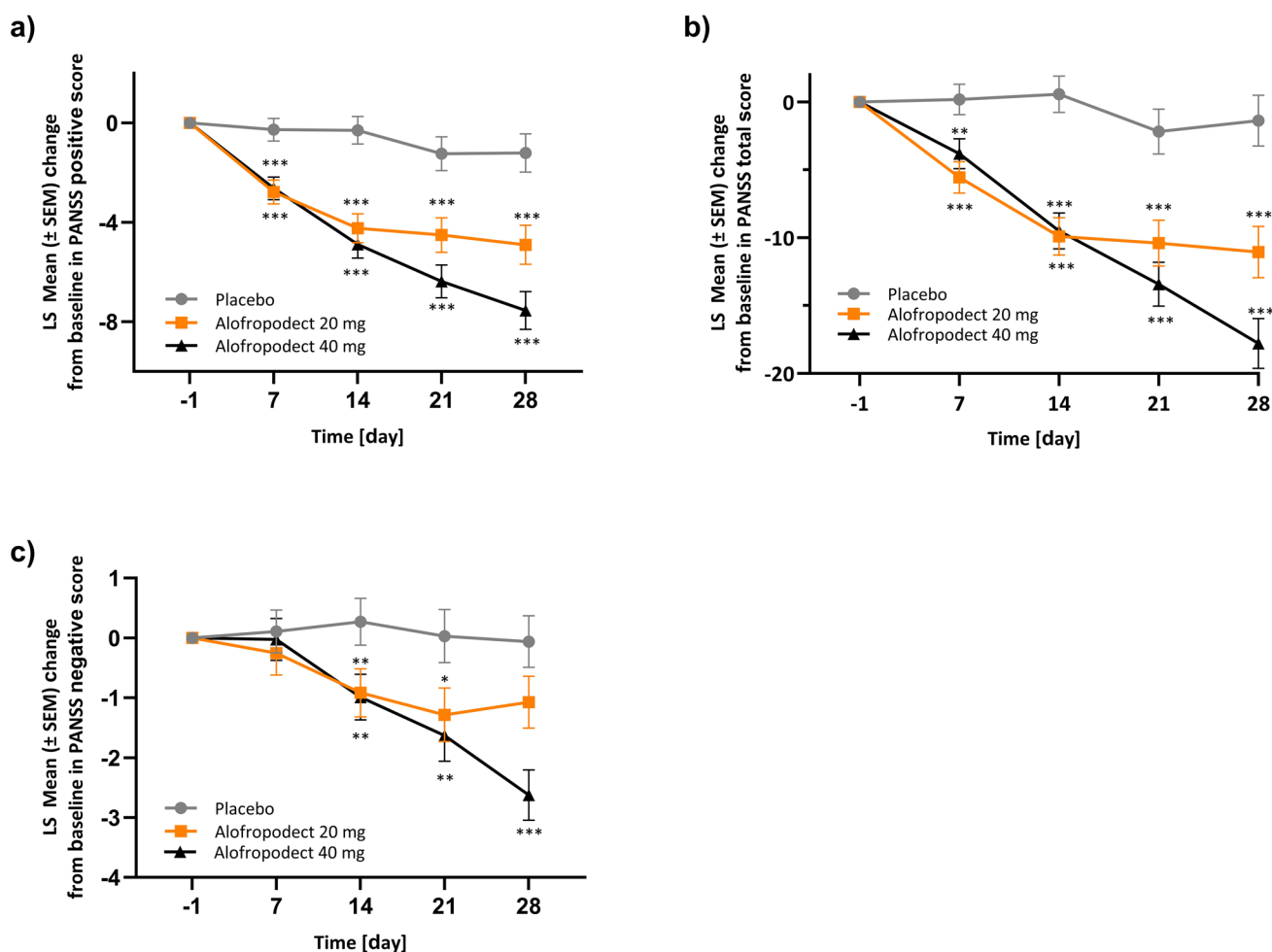


**Fig. 2** CfB in PANSS scores up to week 4 (day 28) for placebo and alofropodect treatment groups in FAS population **a** CfB in mean PANSS positive score; **b** CfB in mean PANSS total score; **c** CfB in mean PANSS negative score; \*nominal  $p < 0.05$ ; \*\*nominal  $p$

$< 0.01$ , \*\*\*nominal  $p < 0.001$ . CfB change from baseline, FAS full analysis Set, LS mean least-squares mean, PANSS positive and negative syndrome scale, SEM standard error of the mean

( $t_{1/2}$ ) ranged from 4.2 to 14.1 h, although sampling may not have been long enough to characterise  $t_{1/2}$  properly. Steady-state was reached by day 5 at the latest. Comparable concentrations of alofropodect were observed on days 7 and 28 for the pre-dose and the 2-h samples. The mean accumulation ratio of alofropodect after once-daily dosing was 1.8 to 3.4, and for a considerable group of participants, no accumulation was observed.

## 4 Discussion

The results of our study indicate that alofropodect, at the fixed doses of 20 and 40 mg, is an effective and well-tolerated treatment for patients experiencing an acute exacerbation of chronic schizophrenia. Both doses produced significant improvement on the PANSS positive subscale score (primary outcome). Significant improvements were also observed across multiple

secondary endpoints, including PANSS total, PANSS negative, PANSS general psychopathology and M5M subscales. The effect size of improvement was moderate for the 20 mg dose and large for the 40 mg dose.

Although the trial was not specifically powered to elucidate this, the 40 mg dose consistently showed greater efficacy than the 20 mg dose, possibly indicating a dose-response pattern. The onset of significant improvement on the PANSS scale typically occurred within the first or second week. A nominal improvement was detected in the treatment groups compared with placebo in neurocognitive measures assessed by the BACS. We presume that the study's timeframe was too short to observe significant improvements in cognition.

Our results contrast with the phase 2 results of other PDE10A inhibitors. Only TAK-063 and MK-8189 have shown partial efficacy, either in secondary endpoints or one of the randomised phase 2 studies of acute schizophrenia. These failures have

**Table 2** Summary of participants with at least one adverse event by randomised treatment of alofropodect or placebo (safety set)

| Category                                                                                                                   | Placebo<br>( <i>N</i> = 65)<br><i>N</i> (%) | Alofropodect 20 mg<br>( <i>N</i> = 57)<br><i>N</i> (%) | Alofropodect 40 mg<br>( <i>N</i> = 65)<br><i>N</i> (%) |
|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Adverse event (AE)                                                                                                         | 25 (38.5%)                                  | 31 (54.4%)                                             | 40 (61.5%)                                             |
| Pre-treatment AE                                                                                                           | 10 (15.4%)                                  | 4 (7.0%)                                               | 10 (15.4%)                                             |
| Serious AE (SAE) <sup>a</sup>                                                                                              | 1 (1.5%)                                    | 1 (1.8%)                                               | 3 (4.6%)                                               |
| Treatment-emergent AE (TEAE)                                                                                               | 22 (33.8%)                                  | 29 (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 TEAE <sup>b</sup>                                                                                                  | 9 (13.8%)                                   | 17 (29.8%)                                             | 20 (30.8%)                                             |
| Related severe TEAE                                                                                                        | 1 (1.5%)                                    | 4 (7.0%)                                               | 2 (3.1%)                                               |
| TEAEs leading to interruption of the drug                                                                                  | 0 (0.0%)                                    | 1 (1.8%)                                               | 0 (0.0%)                                               |
| TEAE leading to permanent discontinuation of study medication                                                              | 3 (4.6%)                                    | 2 (3.5%)                                               | 7 (10.8%)                                              |
| Related TEAEs leading to permanent discontinuation of study medication                                                     | 2 (3.1%)                                    | 1 (1.8%)                                               | 5 (7.7%)                                               |
| AEs that occurred in at least 5% of participants receiving alofropodect, and with a higher incidence compared with placebo |                                             |                                                        |                                                        |
| Anxiety                                                                                                                    | 6 (9.2%)                                    | 6 (10.5%)                                              | 9 (13.8%)                                              |
| Worsening of Schizophrenia                                                                                                 | 2 (3.1%)                                    | 4 (7.0%)                                               | 7 (10.8%)                                              |
| Somnolence                                                                                                                 | 0 (0.0%)                                    | 9 (15.8%)                                              | 8 (12.3%)                                              |
| Blood creatine phosphokinase increased                                                                                     | 1 (1.5%)                                    | 3 (5.3%)                                               | 1 (1.5%)                                               |
| EPS                                                                                                                        | 0 (0.0%)                                    | 4 (7.0%)                                               | 8 (12.3%)                                              |

AE adverse event, EPS extrapyramidal symptoms (includes akathisia, extrapyramidal disorder, dystonia, tremor and psychomotor hyperactivity), *N* number of patients, SAE serious adverse event, SD standard deviation, TEAE treatment emergent adverse event, TESAE treatment emergent serious adverse event

<sup>a</sup>Including pre-treatment SAEs

<sup>b</sup>Any AE with a relationship to study treatment determined by the investigator as ‘unlikely,’ ‘possible,’ ‘probable,’ ‘definite’ or missing is considered related for purposes of analysis

concerned the research community regarding the value of PDE10A as a therapeutic target in schizophrenia, even though strong preclinical results had previously been presented. Preclinical experiments suggested that 20–40% of PDE10A occupancy should be sufficient to exert an antipsychotic effect. That level of inhibition was targeted by other PDE10A inhibitors in clinical development programs [22].

Given our dose-dependent plasma exposure and safety profile up to 100 mg daily (Phase 1 study), we tested the efficacy of alofropodect at 20 and 40 mg. We targeted a higher enzyme occupancy to ensure a sustained target inhibition and provide a robust antipsychotic effect, as reported for MK-8189 [15] and simulated for alofropodect using the PBPK model (Supplementary Appendix 6).

Another contributing factor to the successful phase 2 trial of alofropodect compared with other PDE10A inhibitors may lie in its molecular properties. What is known so far is that PDE10A inhibition modulates the activity of both direct and indirect corticostriatal circuits. It is thought that the opposite action of these pathways belies the importance of an appropriate balance between action in these circuits as a provider of antipsychotic action [23]. Alofropodect exhibits a unique

pharmacodynamic profile, with dose-dependent catalepsy in preclinical studies, unlike other PDE10A inhibitors [18]. This observation suggests a shift in the activation balance towards the indirect pathway, potentially indicating an extended and more pronounced therapeutic efficacy window.

Alofropodect was well-tolerated in the studied population, with only a few SAEs. Status epilepticus occurred in one participant in the 40 mg group. Since seizure frequency is increased in patients with schizophrenia, this case could be disease- rather than drug-induced, but the possibility cannot be excluded that alofropodect may lower the seizure threshold. Seizure risk induction by antipsychotics is well known and attributable to 0.5–3% of patients treated with clozapine, risperidone or olanzapine [24, 25].

We observed a relatively low placebo response in our study, with the largest change from baseline at week 4 (LS mean change – 1.4 for PANSS total). This effect contrasts with most published studies, where a placebo response is typically observed around 10, albeit with high variability. Most of the factors identified as associated with a lower placebo response rate, both in patients’ characteristics and in trial design, were implemented in this study. These factors

include: relatively low sample size, a higher percentage of participants randomised to the placebo group, a small number of sites (MK-8189 used 31 centres in the phase 2a trial, nearly triple alofropodect's 11) and older patients with a long disease history [26–30].

Clinical centres and investigators specialising in the treatment of psychotic disorders were selected, and all raters were trained centrally by an external vendor to maximise standardisation of the patient assessment. All these factors may contribute to a lower placebo response rate in our study.

Another significant impact in our study could have come from the severity of the disease (PANSS score approximately 105), which was higher than the typical range of 85–95 in other studies. This more severe disease at baseline could limit the number of patients, which is inflated at the time of study enrolment. Such inflation of the baseline score to meet patient eligibility requirements, typically set at a PANSS total score of more than 80, is a well-described factor associated with a high placebo response rate [31]. Hence, the combination of the severity of the patients' disease and the large effect size of alofropodect observed in both active arms was probably the main driver of the small placebo effect in our study [30, 32]. The rational study design, described in the not-overcomplicated study protocol, coupled with well-monitored adherence and therapeutic environments, was also crucial in minimising placebo response [33].

Analysis of placebo response by country did not show significant differences in any PANSS subscale at week 4 (e.g., PANSS total LS mean change – 1.9 for Polish sites and – 1.1 for Ukrainian sites), thus, excluding the assumption that the stress factor, which is undoubtedly the war conflict in Ukraine, could have had a significant impact on the strength of the patients' clinical response.

Discontinuation rates were similar between placebo and the treatment arms, although the 40 mg group had a higher discontinuation rate owing to AEs. The intensity of EPS was mild-to-moderate and without a specific pattern. The akathisia was low, with a presentation in two participants in the 20 mg group. There were three discontinuations of treatment owing to EPS in the 40 mg group. Thus, EPS were not a major concern in the study, but should be cautiously evaluated in the further clinical development program. Somnolence occurred at a similar frequency in both active groups. The majority of somnolence presented early (within the first few days) after alofropodect administration and diminished.

Our results suggest that administration of alofropodect over 28 days does not lead to metabolic or hormonal side effects. We observed no increase in lipid or glucose levels, suggesting a mild or neutral metabolic and hormonal profile. We did not specifically test weight change; however, weight reduction was observed in previous animal experiments (manuscript in preparation). Weight reduction was observed

clinically with another PDE10A inhibitor, MK-8189, in a randomised phase 2 studies [15, 16].

Study design and blood sampling schedule enabled a general overview of alofropodect pharmacokinetics in patients with schizophrenia. PK parameters were generally comparable to those observed in healthy volunteers and support once-daily dosing of alofropodect. Accumulation and time to reach steady-state were similar to those observed in healthy volunteers during Phase 1 study. (data on file; Celon Pharma S.A.)

The study was conducted exclusively at clinical sites in Poland, Hungary and Ukraine, which may limit the generalisability. These countries have limited access to advanced medical treatments, particularly in Ukraine, owing to the ongoing military conflict. Only hospitalised patients with moderate-to-severe disease were included, which may limit the generalisability of the results to less ill and more stable patients. The 4-week administration period may not be sufficient to capture the complete safety profile of the molecule. Some PK parameters were calculated only for the extensive-sampling group, and the number of observations per dose level was limited.

## 5 Conclusions

To our knowledge, we present the first evidence of the successful completion of a phase 2 trial with a PDE10A inhibitor in patients with schizophrenia. Alofropodect at fixed doses of 20 mg and 40 mg shows clinically significant improvement in the primary endpoint (PANSS positive score) and most secondary endpoints. The study confirmed alofropodect's favourable safety profile, as observed in healthy subjects, and showed no metabolic or hormonal side effects after 28 days of treatment.

PK parameters were comparable to those observed in healthy volunteers. The study results provide a strong foundation for confirmatory phase 3 trials. Keeping in mind the limited number of study participants, alofropodect appeared to effectively target the PDE10A pathway, showing promising therapeutic potential for schizophrenia and possibly other psychiatric and neurological disorders.

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## Declarations

**Authors’ contributions** Conceptualisation and design: MW, NW, MM, SJ and JSP. Methodology and data collection: NW, EGH, JMR, MP, YF and YB. Pharmacokinetic analysis and interpretation: RJ and PJR. Data acquisition and statistical analysis: JSP, RJ, PJR and BŁ. Writing MW, JSP, PJR, RJ and MM. Review and editing: MW, NW, EGH, JMR, MP, YF, YB, MM, SJ, PJR, RJ, JSP and BŁ. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

**Conflicts of interest** MW is a founder, chief executive officer and majority owner of Celon Pharma S.A. and holds stocks in Celon Pharma S.A. MM, PJR, RJ, BŁ and JSP are employees (or were employees during the trial) of Celon Pharma S.A., received a salary and may hold stocks. SJ is a former employee of Celon Pharma S.A., currently employed by Eli Lilly Cork Ltd. and declares stock ownership of Celon Pharma S.A. and Eli Lilly. All other authors declare no competing interests.

**Ethics approval** The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice guidelines for biomedical research. The protocol and informed consent were approved by the appropriate institutional review boards or independent ethics committees (Supplementary Appendix 1).

**Consent to participate** Participation and any study-related procedures began only after each participant had signed the written informed consent form (ICF).

**Consent for publication** Not applicable.

**Availability of data and material** The data that support the findings of this study are available upon reasonable request. Requests to access the datasets should be directed to [marta.maciejak@celonpharma.com](mailto:marta.maciejak@celonpharma.com).

**Code availability** Not applicable.

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## Authors and Affiliations

Maciej Wieczorek<sup>1</sup>  · Napoleon Waszkiewicz<sup>2</sup>  · Ewa Gromniak-Haniecka<sup>3</sup> · János M. Réthelyi<sup>4</sup>  · Mykhaylo Pustovoyt<sup>5</sup>  · Yuriy Filts<sup>6</sup>  · Yuliya Blazhevych<sup>7</sup>  · Mikołaj Małłoka<sup>1</sup>  · Sylwia Janowska<sup>1</sup> · Barbara Łapińska<sup>1</sup>  · Piotr J. Rudzki<sup>1</sup>  · Radosław Jaźwiec<sup>1</sup>  · Joanna Sierzputowska-Prarat<sup>1</sup> 

✉ Joanna Sierzputowska-Prarat  
joanna.sierzputowska@celonpharma.com

- <sup>1</sup> Research and Development Centre, Celon Pharma S.A., Kuzuń Nowy, Poland
- <sup>2</sup> Department of Psychiatry, Medical University of Białystok, Białystok, Poland
- <sup>3</sup> Provincial Psychiatric Health Hospital named after Dr Józef Bednarz in Świecie, Świecie, Poland
- <sup>4</sup> Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

- <sup>5</sup> Department of Psychiatry, Narcology and Medical Psychology, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine
- <sup>6</sup> Lviv Regional Clinical Psychiatric Hospital, Lviv, Ukraine
- <sup>7</sup> Communal Non-commercial Enterprise “Clinical Facility for Mental Health Care ‘PSYCHIATRY’” of the executive body of Kyiv City Council (Kyiv City State Administration), Center of First Psychotic Episode and Novel Methods of Treatment, Kyiv, Ukraine