Clinical Study Report

Effects of early clozapine treatment on remission rates in acute schizophrenia (EARLY)

A multicentre, randomized, double-blind, parallel group interventional phase III clinical trial

Investigational Medicinal Product:
Clozapine, Olanzapine

Study Code: EARLY_KUM_PSY

EudraCT Number: 2018-001514-15

First Patient First Visit: 17.06.2019 **– Last Patient Last Visit:** 28.01.2025

Sponsor
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vertreten durch
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Synopsis

1.	**Sponsor:** Bezirkskliniken Schwaben Geschwister-Schönert-Straße 4, 86156 Augsburg **Sponsor Delegated Person (SDP):** Prof. Dr. med. Alkomiet Hasan
2.	**Name of Finished Product:** Clozapine, Olanzapine
3.	**Name of Active Ingredient:** Clozapine, Olanzapine
4.	**Individual Study Table:** (only required for submissions) NAP
5.	**Study Title:** Effects of early clozapine treatment on remission rates in acute schizophrenia (EARLY)
	Study Design: EARLY is a multicenter, randomized, double-blind, controlled clinical trial comparing early introduction of clozapine with olanzapine in patients with acute schizophrenia.
	Study (Protocol) Code Number: EARLY-KUM-PSY
	Eudra-CT Number: 2018-001514-15
6.	**Investigators:** # 1: Prof. Dr. med. Peter Falkai # 2: Prof. Dr. med. Tilo Kircher # 4: Dr. med. David Prvulovic # 5: Dr. med. Berthold Langguth # 6. Dr. med. Kathrin Eckstein # 7: Prof. Dr. med. Alkomiet Hasan # 8: Bettina Klos # 9: Thorsten Nolting # 11: Prof. Dr. med. Dusan Hirjak
7.	**Participating Clinical Trial Sites:** # 1 Klinik für Psychiatrie und Psychotherapie, Klinikum der Universität München, Nußbaumstraße 7, 80336 München # 2: Klinik für Psychiatrie und Psychotherapie, Universitätsklinikum Gießen und Marburg GmbH, Standort Marburg, Rudolf-Bultmann-Straße 8, 35039 Marburg # 4: Klinik für Psychiatrie, Psychosomatik und Psychotherapie, Universitätsklinikum Frankfurt, Heinrich-Hoffmann-Str. 10, 60528 Frankfurt # 5 Klinik und Poliklinik für Psychiatrie und Psychotherapie der Universität Regensburg am medbo Bezirksklinikum Regensburg, Universitätsstr. 84, 93053 Regensburg # 6: Universitätsklinikum Tübingen, Klinik für Psychiatrie und Psychotherapie, Calwerstr. 14, 72076 Tübingen # 7: Bezirkskrankenhaus Augsburg, Klinik für Psychiatrie, Psychotherapie und Psychosomatik der Universität Augsburg, Geschwister-Schönert-Straße 4, 86156 Augsburg # 8: Rheinhessen-Fachklinik Alzey, Abteilung 1 für Allgemeinpsychiatrie, Psychotherapie und Psychosomatik, Dautenheimer Landstr. 66, 55232 Alzey # 9: LVR-Klinikum Düsseldorf der HHU DÜS, Allgemeine Psychiatrie, Klinik für Psychiatrie und Psychotherapie, Bergische Landstr. 2, 40229 Düsseldorf

	# 11: Zentralinstitut für Seelische Gesundheit, Klinik für Psychiatrie und Psychotherapie, J5, 68159 Mannheim Closed clinical trial sites without recruiting patients (#3, #10) are not listed.
8.	**Publication**: Effects of Early Clozapine Treatment on Remission Rates in Acute Schizophrenia (The EARLY Trial): Protocol of a Randomized-Controlled Multicentric Trial. Pharmacopsychiatr. 2023 Sep;56(5):169-181. doi: 10.1055/a-2110-4259.
9.	**Study period:** First patient first visit: 17.06.2019; last patient included: 04.11.2024; last patient last visit: 28.01.2025.
	Approvals and Amendments: **First Submission:** Approval: Bundesinstitut für Arzneimittel und Medizinprodukte（BfArM): 10.12.2018; Ethics Committee (EC): 07.12.2018; clinical study protocol (CSP) Version 2.0 15.11.2018 There were various changes in clinical trial sites/investigators/their deputies during the conduct of the clinical trial. Substantial changes resulting in a revision of CSP/change of sponsor: **Amendment 1**: The following major changes were included in AM 1: the CSP was adapted for timelines, wording modifications/additions to improve understanding e.g. of handling IMP, conduct of visits. Approval AM1: BfArM: 02.05.2019; EC: 02.05.2019; CSP Version 3.0 20.02.2019 [CSP Version 3.1. 09.05.2019 (minor edit. changes): acknowledgement EC 24.05.2019] **Amendment 2:** The following major changes were included in AM 2: inclusion # 5 changed to reflect different therapies of schizophrenia prior to inclusion of patients, opening time frame for assessments of IMP plasma levels and documenting this change in timing of blood withdrawal, changing definition of one secondary endpoint to “other assessment”, specifications/adaptation of: exclusion # 7, legal representative, V10-V13, potential increase in IMP dependent on white blood count, concomitant medications. Approval AM2: BfArM: 12.11.2019; EC: 14.11.2019, CSP Version 4.0, 21.10.2019 **Amendment 3:** The following major changes were included in AM 3: change in sponsor from Klinikum der Universität München to Bezirkskliniken Schwaben, inclusion #5 was changed to allow patients who were treated with olanzapine (if this had not been longer than two weeks prior to inclusion). Approval AM3: BfArM: 17.12.2020; EC: 14.12.2020, CSP Version 5.0, 30.11.2020 **Amendment 4:** The following major changes were included in AM 4: new manufacturer for clozapine: 1A-Pharma (former HEXAL), adapted wording in CSP. Approval AM4: BfArM: 06.12.2022; EC: 06.12.2022, CSP Version 6.0, 11.11.2022 **End of recruitment:** Response to end of recruitment (15.11.2024) was received from BfArM: 25.11.2024; EC: 18.11.2024. **End of clinical trial:** Acknowledgement of end of the clinical trial (30.01.2025) was received from EC: 31.01.2025
10.	**Phase of development:** Phase III
11.	**Objectives:**

	Primary Objective: To investigate the symptomatic remission rates in non-treatment-refractory patients with schizophrenia randomized to either early clozapine or olanzapine over an 8-week period. **Secondary Objectives:** include differences in side effects, symptom severity, safety measures and cognitive functions.
12.	**Background/Methodology:** Achieving symptomatic remission quickly after the onset of psychotic symptoms is the critical objective in schizophrenia treatment and determines the subsequent disease course. In this context, only every second patient with acute schizophrenia achieves symptomatic remission within three months of initiating antipsychotic treatment, meaning that half of the patients do not achieve this key objective. Increasing the likelihood to achieve symptomatic remission in acute schizophrenia will improve the overall outcome, reduce disease-associated burden and potentially prevent mid- and long-term disease chronicity. With this randomized, double-blind, parallel-group multicentre trial we aimed to provide evidence for the superior efficacy of the 'last resort' antipsychotic clozapine compared to one of the most effective second-generation antipsychotics (SGAs), olanzapine, in acute schizophrenia patients who do not meet the criteria for treatment-naive or treatment-resistant schizophrenia. Our target population represented the largest group of schizophrenia patients; these patients are frequently hospitalized and receive ~20% of all psychiatric inpatient treatments in Germany. A total of 220 patients from several departments of psychiatry with acute schizophrenia were planned to be randomized to a double-blind, eight-week treatment with either clozapine or olanzapine. The primary endpoint was defined as the number of patients in symptomatic remission at the end of week eight according to the international consensus criteria ('Andreasen criteria'). Secondary endpoints and other assessments include e.g. symptom severity, disease severity, global functioning, cognition, side-effect dimensions and patients' and relatives' view on treatment. The clinical trial is registered at the EU Clinical Trials Register and DRKS - Deutsches Register Klinischer Studien (identifier: DRKS00016043). Figure 1 displays a schematic study flow-chart.

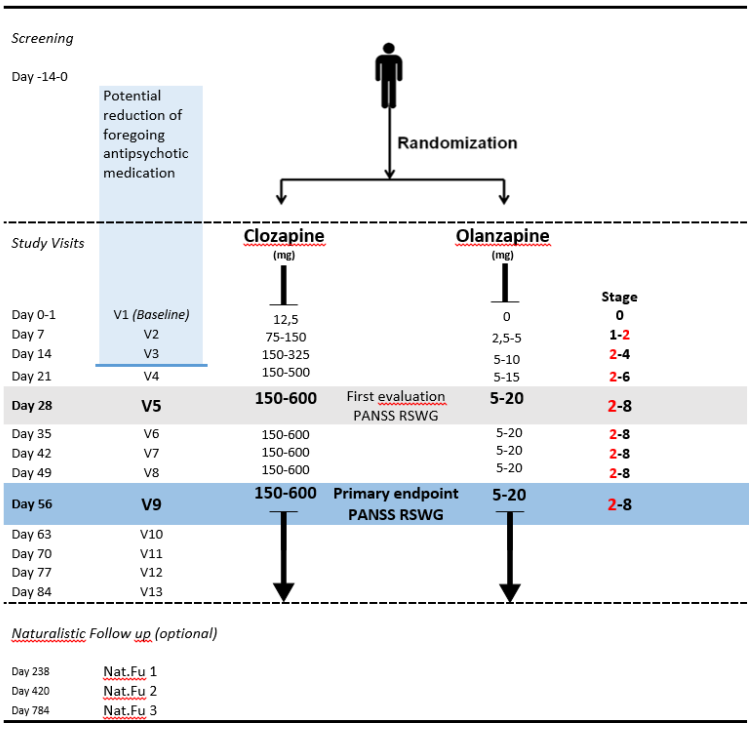


Figure 1: Schematic Study Flow-Chart, IMP scheme; legend: BL= baseline

13.	**Sample size (planned/analysed):** Planned: To be assessed for eligibility: n = 880 patients To be allocated to trial: n = 220 patients To be analysed at 2 months (ITT): n = 220 (n = 110 in each study group) Analysed: Randomized: 75 patients Intent-to-Treat (ITT) population: 71 patients Safety set: 74 patients Per-protocol (PP) population: 53 patients
14.	**Patient Population (Diagnosis):** ICD10: F20 Gender: both male and female Minimum age: 18 years; maximum age: 65 years These definitions were applied for all analysis populations, ITT, PP and safety set.
	Main criteria for inclusion: 1. Age 18 to 65 years 2. Signed informed consent 3. DSM-V diagnosis of schizophrenia confirmed by the Mini international Neuropsychiatric Interview 4. At least one documented prior hospitalization due to the illness in the medical history (the current hospitalization can be considered as “prior” hospitalization if its ≥ 4 weeks) at screening 5. For treatment-naïve patients (defined as no previous antipsychotic treatment or a maximum of 30 days of treatment), an antipsychotic treatment attempt of at least 30 days with an antipsychotic in a therapeutic dose according to local guidelines other than clozapine and olanzapine before the screening phase is needed. For non-treatment-naïve patients (defined as having been treated for more than 30 days with an antipsychotic), a discontinuation of a foregoing antipsychotic treatment prior to the screening phase within a maximum of six months (=180 days) is possible (corresponding to the estimated average time for an antipsychotic washout phase and the expected time to develop a relapse of the disease). For patients being treated with a long-acting antipsychotic (other than PP3M), an inclusion is possible if inclusion date corresponds to the planned date of the next injection plus five to seven days. For patients being treated with oral olanzapine, an inclusion is possible if this treatment has lasted for no longer than 2 weeks prior to inclusion and if exclusion criteria 8 is not fulfilled. 6. Clinical need for a medication switch because of clinical inefficacy or side-effects or clinical need for a reintroduction of an antipsychotic treatment after treatment discontinuation prior to the screening phase (see 5.) 7. Moderate symptomatology on the PANSS, defined as a score ≥ 4 for two or more symptoms from P1-P7 or a score of ≥ 6 for one symptom from P1-P7 (minimum threshold definition) at screening 8. Male participants and female participants who are not capable of bearing children or who use a method of contraception that is medically approved by the health authority of the respective country at screening

	Main criteria for exclusion: 1. Patients who are not suitable for the study in the opinion of the investigator 2. Patients who are unable to give informed consent 3. Coercive treatment at the time of study inclusion 4. White blood cell count (WBC) at inclusion not meeting the requirements for clozapine use in Germany. Patients must have normal leukocyte findings (white blood cell count ≥ 3500/mm^3 (≥ 3.5x10^9/l), and Absolute Neutrophil Count (ANC) ≥ 2000/mm^3 (≥ 2.0x10^9/l) at the screening visit 5. The presence of one or more of the contraindications against any of the study drugs as mentioned in the SmPC 6. Treatment-naïve or treatment-resistant schizophrenia. Treatment-naïve will be defined as no previous antipsychotic treatment or a maximum of 30 days of treatment. Treatment resistance is defined as 2 antipsychotic trials (with antipsychotics from two different chemical classes) for a period of ≥ 6 weeks with CPZ equivalent doses ≥ 600 mg/day, both of which took place immediately before the screening phase 7. Diagnosis of primary substance dependency other than nicotine 8. Documented previous non-response to an 8-week drug trial with olanzapine or any documented previous treatment with clozapine 9. Intolerance to one of the study drugs 10. Pregnancy (incl. positive blood pregnancy test) / lactation (female patients).
15.	**Test product, dose and mode of administration:** To maintain blinding, patients in the olanzapine arm received placebo tablets on the first day and, during the titration period, take olanzapine together with placebo, so that the dosing schedule mimics the clozapine regimen. This ensures that treatment, appearance and administration are indistinguishable between study arms. Eligible patients are randomized 1:1 to receive either clozapine or olanzapine (plus placebo as needed) for an 8-week treatment period. **Experimental intervention**: Application of double-blind early **clozapine** (after starting dose of 12,5 titrated to a total of 150 - 600 mg administered in two capsules daily) in acute schizophrenia patients not meeting the criteria for treatment resistance (group 1). **Control intervention**: Application of double-blind **olanzapine** (after a starting dose from 2,5 titrated up to a total of 5 - 10 mg administered in two capsules daily) in acute schizophrenia patients not meeting the criteria for treatment resistance (group 2). **Placebo** Placebo as needed for blinding the titration phase. **Batch-No. (Ch.-B):** EARLY/201911-W, EARLY/201911-G, EARLY/201911-R, EARLY/201911-B, EARLY/202002-W, EARLY/202002-G, EARLY/202002-R, EARLY/202002-B, EARLY/202029-W, EARLY/202029-G, EARLY/202029-R, EARLY/202029-B, EARLY/202105-W, EARLY/202105-G, EARLY/202105-R, EARLY/202105-B, EARLY/202138-W, EARLY/202138-G, EARLY/202138-B, EARLY/202147-W, EARLY/202147-G, EARLY/202221-W, EARLY/202221-G, EARLY/202249-R, EARLY/202308-B, EARLY/202309-W, EARLY/202309-G, EARLY/202334-W, EARLY/202334-G, EARLY/202347-R, EARLY/202347-B, EARLY/202428-W, EARLY/202428-G
16.	**Duration of administration:** Maximum of 56 days (V1-V9)
17.	**Background therapy:** Standard of care **Comparator**: NAP
	Blinding: Double-blind (randomization lists were created using RANCODE 2015 professional 2015)

18.

Criteria for evaluation:

Primary endpoint: is the relative frequency of patients in the clozapine group in remission (according to remission in Schizophrenia Working Group [RSWG] consensus criteria) at week eight (V9) compared to the olanzapine group.

Dimension of psychopathology	PANSS Item number	Criterion	Score for remission
Psychoticism (reality distortion)	Delusions	P1	≤ 3
	Unusual thought content	G9	≤ 3
	Hallucinatory behaviour	P3	≤ 3
Disorganization	Conceptual disorganisation	P2	≤ 3
	Mannerisms/posturing	G5	≤ 3
Negative symptoms	Blunted affect	N1	≤ 3
	Social withdrawal	N4	≤ 3
	Lack of spontaneity	N6	≤ 3

Table 1: RSWG criteria for remission (primary endpoint) (Andreasen, Carpenter et al. 2005)

Secondary endpoints: The following measures will be compared between study arms:

- Relative frequency of patients in remission after four weeks (V5) according to the RSWG criteria (Andreasen, Carpenter et al. 2005).
- Change in Positive and Negative Syndrome Scale (PANSS) total and in the three PANSS subscales (positive, negative, general) from baseline (V1) to week four (V5) and week eight (V9)
- Frequency of patients in remission according to the RSWG criteria without the negative symptom Items (N1, N4 and N6) after four (V5), six (V7) and eight weeks (V9)
- Frequency of patients with a clinical response according to PANSS (≥ 20% change from baseline, corrected PANSS formula) (Leucht 2014) after four (V5) and eight weeks (V9).

<u>Secondary endpoints regarding side-effects and safety</u>:

- Change in white/complete blood count (WBC/CBC), creatinine kinase (CK) blood levels from screening (V0) to every visit during the study period (V13).
- Relative change in Troponine, frequency of 2-fold elevated Troponine, and absolute change in C-reactive protein (CRP) values from screening to every visit during the first four weeks of the intervention period (V1-V5) and at week 6 (V7) and week eight (V9).
- Changes in standard parameters of Electrocardiography (ECG) (QT interval-value, heart rate value from screening/baseline (V1) to week 2 (V3), week 4 (V5), week 6 (V7) and week eight (V9).

<u>Other clinical assessments</u>:

- Relationship between drug blood levels/concentration (central laboratory KUM) and clinical and side-effect endpoints.
- Change in physical examinations from baseline (V1) to every visit during the intervention period (V9).
- Change in Thought and Language Disorder (Kircher, Krug et al. 2014) (TALD, total scores of 30 items, each item ranging from 0-4 points) (Kircher, Krug et al. 2014) from baseline (V1) to week eight (V9).
- Change in Clinical Global Impression scale (CGI) (Endicott, Spitzer et al. 1976) score (scores from 1-7) from baseline (V1) to week four (V5) and week eight (V9) and to the follow-up visits.

	• Change in Personal and Social Performance scale (PSP) (total score from 1-100) (Nasrallah, Morosini et al. 2008) from baseline (V1) to week eight (V9) and to the follow-up visits. • Change in Global Assessment of Functioning scale (GAF) scores (total score from 0-100) from baseline (V1) to week four (V5) and week eight (V9). • Change in Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington et al. 1993) total score (total score from 0-27) from baseline (V1) to week four (V5) and week eight (V9). • Trail-Making Test A and B (total scores for speed and errors). Change in total TMT scores from baseline (V1) to week eight (V9). • Change in suicidal ideations based on the InterSePT scale (ISST) (total score) (Lindenmayer, Czobor et al. 2003) from baseline (V1) to week eight (V9). • Change in quality of life measures according to the abbreviated quality of life enjoyment and satisfaction questionnaire (Q-LES-Q-18) (total score) (Ritsner, Kurs et al. 2005) from baseline (V1) to week eight (V9) and to the follow-up visits. • Change in SF-12 score items (12 separate items) (Ware, Kosinski et al. 1996) from baseline (V1) to week eight (V9). • Change in Drug Attitude Inventory (DAI10) (total score) (Stjernsward, Persson et al. 2013) scores from baseline (V1) to week eight (V9). • Change in Subjective Wellbeing under Neuroleptics short form (SWN-K) (Naber 1995) (Naber 1995) total score (from baseline (V1) to week eight (V9). • Attitude of patients towards participation in clinical research and towards the treatment with olanzapine and clozapine at baseline (self-developed questionnaire) in collaboration with BApK (a relatives-driven pan-organisation that represents the interests of relatives and persons affected by mental illness) at screening. Here, a likert-scale will be used to present descriptive statistics. <u>Other assessments regarding side-effects and safety:</u> • Changes in blood pressure and heart rate (values) from baseline (V1) to every visit during the intervention period (V9). • Changes in Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS for Clozapine) (Hynes, Keating et al. 2015) scores from baseline (V1) to week 2 (V3), week 4 (V5) and week eight (V9). • Changes in the St Hans Rating Scale (SHRS) (Gerlach, Korsgaard et al. 1993) (Gerlach, Korsgaard et al. 1993) scores from baseline (V1) to week eight (V9). • Week eight Changes in Cleveland Clinic Constipation Score (CCCS) (Agachan, Chen et al. 1996) scores from baseline (V1) to week 2 (V3), week 4 (V5) and week eight (V9). • Changes in the Barnes Akathisia Rating Scale (BARS) (Barnes 1989) scores from baseline (V1) and week eight (V9). • Change in fasting glucose, cholesterol, HDL (values) from baseline (V1) to week 4 (V5) and week eight (V9). • Change in weight and BMI from baseline (V1) to week four (V5) and week eight (V9). • Change in number of cigarettes from baseline (V1) to week two (V3), week four (V5), week five (V6) and week eight (V9). • Changes in standard parameters of Electroencephalography (EEG) (e.g. frequency bands) from baseline (V1) to week eight (V9).
	Efficacy: Efficacy assessments follow endpoint analyses.
	Safety assessments: Safety assessments follow endpoint analyses and were assessed from the start of the intervention (V1) until end of study V13 (84 days after baseline). An independent Safety Monitoring Board supported review of safety data and trial progress.

19. **Statistical methods:**

Population for analysis

The final definition of the ITT analysis population differs from the definition in the clinical trial protocol. According to ICH E9 'There are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication and the lack of any data post randomisation'. Such exclusion does not introduce bias if 'the entry criterion was measured prior to randomisation', 'the detection of the relevant eligibility violations can be made completely objectively', 'all subjects receive equal scrutiny for eligibility violations', 'all detected violations of the particular entry criterion are excluded'. In adherence to these requirements, it was decided in a blinded data review meeting, that all subjects with eligibility violations prior to randomisation, failure to take the trial medication or no data post randomisation are to be excluded from the ITT analysis set.

Intention-to-Treat (ITT) Population: all randomized patients, except those with eligibility violations prior to randomization, failure to take the trial medication, or no data post-randomisation, and is analyzed according to the intention-to-treat principle. Patients will be assigned to the treatment group to which they were randomized, regardless of the actual treatment received or protocol deviations.

Per-protocol Population (PP): subset of the ITT population excluding patients with major protocol deviations that could affect the efficacy evaluation.

Safety Set: Includes all patients who received at least one dose of study medication. Patients will be analysed according to the treatment actually received.

Confidence intervals and p-values: All hypothesis tests will be two-sided with a significance level of 5%. Confidence intervals (CI) will be reported at the 95% level. No adjustments for multiplicity will be made for secondary endpoints, which are considered exploratory.

General reporting rules:

- Continuous variables will be summarized by number of observations, mean ± standard deviation (SD) or median (minimum, maximum) as appropriate.
- Categorical variables will be summarized by absolute and relative frequencies.
- Percentages will be based on the number of non-missing values, unless otherwise stated.

Estimands: The primary estimand and its attributes are described in the table below:

Attribute	Description
Population	All randomized patients (ITT)
Variable	Remission status at Week 8 (V9) according to RSWG (Andreasen) criteri without time criterion
Treatment	Clozapine vs. olanzapine (plus placebo as needed for blinding titration)
Population Summary	Difference in remission rates between treatment groups
Intercurrent Events (ICE) - strategies	- Treatment discontinuation – treatment policy - Rescue (antipsychotic) medication – treatment policy - Missing PANSS at Week 8 - hypothetical strategy

Table 2: Primary estimand

ICEs treatment discontinuation and rescue medication were handled using the treatment policy strategy to determine the treatment effect. Missing PANSS assessments for the primary endpoint analysis were handled according to the protocol-defined highly conservative composite variable strategy: patients lost to follow-up in the experimental group were considered non-remitters, while those in the control group were considered remitters.

No other missing values will be imputed.

Primary endpoint analysis

The primary endpoint is the relative frequency of patients in remission (yes/no) at Week 8 (V9) according to the RSWG (Andreasen) criteria without time criterion. Statistical hypotheses: $H_0: \Pi_C = \Pi_O \quad vs. \quad H_A: \Pi_C \neq \Pi_O$, where Π_C and Π_O denote the remission rates at Week 8 in the clozapine and olanzapine groups respectively.

Analysis method: The primary comparison between treatment groups was performed using a chi-square test. The odds ratio with 95% CI were reported. The analyses described above were performed on the ITT and repeated on the PP population. All safety analyses were performed on the safety set.

Secondary endpoint analyses

Secondary endpoints were documented during weekly follow-up visits. Analyses were conducted on the appropriate analysis set according to the type of endpoint as described below.

Secondary endpoints		**Analysis Method**
Analysis sets: ITT, PP		
1	Relative frequency of patients in remission after four weeks (V5) according to the **RSWG** criteria	Chi² test
2	Change in **PANSS** • total • positive • negative • general from baseline (V1) to week four (V5) and week eight (V9)	Linear regression for each sub-score and each time-point, including treatment group and baseline value as covariates. (8 models: 4 sub-scores, two time points)
3	Frequency of patients in remission according to the **RSWG** criteria without the negative symptom Items (N1, N4 and N6) after four (V5), six (V7) and eight weeks (V9)	Chi² test (one test at 3 time points)
4	Frequency of patients with a clinical response according to **PANSS** (≥ 20% change from baseline, corrected PANSS formula) (Leucht 2014) after four (V5) and eight weeks (V9)	Chi² test (one test at 2 time points)
Secondary endpoints regarding side-effects and safety		**Analysis Method**
Analysis set: Safety set		
1	Change in white/complete blood count (**WBC/CBC**), creatinine kinase (**CK**) blood levels from screening (V0) to every visit during the study period (V13).	Mann-Whitney-U test for each lab value at each time point.
2	• Relative change in **Troponine** • frequency of 2-fold elevated Troponine • absolute change in C-reactive protein (**CRP**) values from screening to every visit during the first four weeks of the intervention period (V1-V5) and at week 6 (V7) and week eight (V9).	Mann-Whitney-U test for the relative change in Troponine and change in CRP at each time point. Fisher exact test for the frequency of 2-fold elevated Troponine at each time point.
3	Changes in standard parameters of **ECG** • QTc interval • heart rate from screening/baseline (V1) to week 2 (V3), week 4 (V5), week 6 (V7) and week eight (V9).	Mann-Whitney-U test for each ECG value at each time point.

Other clinical assessments

Analysis sets: ITT

Analysis Method: Analysis using appropriate for the distribution statistical tests (Mann-Whitney-U test or Chi^2 test) for each time point separately.

Other assessments regarding side-effects and safety

Analysis set: Safety set

Analysis Method: Analysis using appropriate for the distribution statistical tests (Mann-Whitney-U test or Chi^2 test) for each time point separately.

20. **Summary - Conclusions:**

Patient demographics and patient disposition

In total 75 patients were included in the study (FPFV: 17.06.2019; LPLV: 28.01.2025. 4 of 75 patients were excluded from the ITT set and 71 patients were analysed. From the 75 patients, 22 were excluded for the PP analysis set that consisted of 53 patients. See supplement for the CONSORT chart and the reasons for exclusion are given in table 1.

Analysis set *(n, %)*	Treatment group				All (N = 75)	
	Clozapine (N = 36)		Olanzapine (N = 39)			
ITT set	34	(94.4 %)	37	(94.9 %)	71	(94.7 %)
Excluded from ITT set						
EC 5 met	0		1	(2.6 %)	1	(1.3 %)
IC 4 not met	0		1	(2.6 %)	1	(1.3 %)
IC 7 not met	1	(2.8 %)	0		1	(1.3 %)
no IMP	1	(2.8 %)	0		1	(1.3 %)
PP set	25	(69.4 %)	28	(71.8 %)	53	(70.7
Excluded from PP set						
EC 5 not met	0		1	(2.6 %)	1	(1.3 %)
IC 4 not met	0		1	(2.6 %)	1	(1.3 %)
IC 7 not met	1	(2.8 %)	0		1	(1.3 %)
Early termination of IMP	9	(25.0 %)	9	(23.1 %)	18	(24.0 %)
no IMP	1	(2.8 %)	0		1	(1.3 %)
Safety set	35	(97.2 %)	39	(100 %)	74	(98.7 %)
Excluded from safety set	35	(97.2 %)	39	(100 %)	74	(98.7 %)
no IMP	1	(2.8 %)	0		1	(1.3 %)

Table 1: Analysis sets

The study visit V9 (time of primary endpoint data collection) was completed by 32/34 (94.1%) patients in Group 1 (clozapine), 32/37 (91.9%) patients in Group 2 (olanzapine) (ITT set).

46 male and 25 female adults were included (ITT set). The median age was 33 (21 to 62) years in group 1 (23 male, 11 female), 33 (18 to 63) years in group 2 (23 male, 14 female).

Distributions of relevant demographics at baseline were similar in both treatment groups. Descriptive statistics are given in Tables 2 and 3.

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Female *(n, %)*	11 (32.4 %)	14 (37.8 %)
German national *(n, %)*	23 (67.7 %)	25 (67.6 %)
Marital Status *(n, %)*		
never married	28 (82.4 %)	32 (86.5 %)
married	4 (11.8 %)	1 (2.7 %)
divorced/legally separated	2 (5.9 %)	3 (8.1 %)

widowed	0	1 (2.7 %)
Educational Level *(n, %)*		
No degree	2 (5.9 %)	1 (2.7 %)
Secondary School	10 (29.4 %)	10 (27.0 %)
Junior High School	7 (20.6 %)	6 (16.2 %)
High School / High School Diploma	5 (14.7 %)	3 (8.1 %)
University/College	4 (11.8 %)	5 (13.5 %)
Apprenticeship	6 (17.7 %)	12 (32.4 %)
Currently working *(n, %)*	7 (20.6 %)	8 (21.6 %)
Living alone *(n, %)*	18 (52.9 %)	21 (56.8 %)
Type of housing *(n, %)*		
house	3 (8.8 %)	6 (16.2 %)
apartment	2 (5.9 %)	5 (13.5 %)
flat	26 (76.5 %)	18 (48.7 %)
therapeutic living	0	3 (8.1 %)
special care home	0	2 (5.4 %)
without a permanent home	1 (2.9 %)	2 (5.4 %)
other	2 (5.9 %)	1 (2.7 %)
Age, years *(median, range)*	33 (21 – 62)	33 (18 – 63)
Number of school years, including apprenticeship/studying *(median, range)*	13 (9 – 20)	13 (9 – 25)
Number of Children *(n, %)*		
None	33 (97.1 %)	35 (94.6 %)
1	1 (2.9 %)	0
2	0	2 (5.4 %)

Table 2: Demographics

	Sex		All
	Male (N = 49)	Female (N = 26)	(N = 75)
Age group, years *(n, %)*			
18 – 19	2 (4.1 %)	1 (3.8 %)	3 (4.0 %)
20 – 29	20 (40.8 %)	8 (30.8 %)	28 (37.3 %)
30 – 39	14 (28.6 %)	7 (26.9 %)	21 (28.0 %)
40 – 49	5 (10.2 %)	7 (26.9 %)	12 (16.0 %)
50 – 59	6 (12.2 %)	3 (11.5 %)	9 (12.0 %)
60 – 69	2 (4.1 %)	0	2 (2.7 %)

Table 3: Age distribution of all patients randomized

Concomitant therapy during the study

All patients received the routine care treatment in the respective participating trial site including pharmacotherapy, psychotherapy, and psychosocial treatments in accordance with the in the protocol defined inclusion and exclusion criteria.

Abuse at current time

Substance abuse is the most frequent comorbidity in patients with schizophrenia. Table 4 shows the distribution in both study groups of secondary substance abuse.

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Substance abuse at BL *(n, %)*		
Yes	5 (14.7 %)	7 (18.9 %)
No	29 (85.3 %)	30 (81.1 %)

Table 4: Distribution of substance abuse at inclusion

Medical history of schizophrenia

Table 5 summarizes relevant medical history information.

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Age at begin of schizophrenia *(median, range)*	24 (12 – 49)	24 (10 – 47)
Days of untreated psychosis before first diagnosis* *(median, range)*	7 (1 – 72)	10 (1 – 216)
Number of hospitalizations due to schizophrenia *(median, range)*	2 (1 – 15)	2 (1 – 40)
Number of episodes& *(median, range)*	2.5 (1 – 5)	3 (2 – 40)
Maximal length of episodes, days~ *(median, range)*	9 (4 – 24)	8 (4 – 24)

** N = 24 (Clozapine); N = 30 (Olanzapine)*
& N = 10 (Clozapine); N = 35 (Olanzapine)
~ N = 10 (Clozapine); N = 13 (Olanzapine)

Table 5: Medical history of schizophrenia.

Comorbidities

Relevant comorbidities are summarized in table 6.

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Pre-existing drug-induced reaction *(n, %)*	26 (76.5 %)	28 (75.7 %)
Previous psychiatric disorders *(n, %)*	31 (91.2 %)	35 (94.6 %)
Severe cranio-cerebral trauma *(n, %)*	1 (2.9 %)	5 (13.5 %)
Impairment of basal ganglia / brain stem *(n, %)*	0	0
Electronic implant *(n, %)*	0	0
Malignant disease *(n, %)*	0	0
Severe active infectious disease *(n, %)*	0	1 (2.7 %)
Chronic and systemic skin disorders *(n, %)*	6 (17.7 %)	5 (13.5 %)
Severe internal medical condition *(n, %)*	20 (58.8 %)	26 (70.3 %)
Bone disease *(n, %)*	8 (23.5 %)	3 (8.1)
Severe neurological disorder *(n, %)*	9 (26.5 %)	5 (13.5 %)

Table 6: Comorbidities.

Compliance:

Protocol Deviations (PD):
165 PD were reported in 55/75 patients. 6 of those PD were classified as major.

Study medication:
Seventy-four of 75 patients of the ITT population received at least one dose of IMP. They are included in the safety analysis set.

Premature termination of IMP intake: 18/71 patients stopped IMP intake prematurely. The reasons for early discontinuation of IMP intake for patients in the ITT set are given in table 7 (multiple reasons were acceptable).

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Premature termination of IMP intake *(n, %)*	9 (26.5 %)	9 (24.3 %)
Reason for premature IMP-intake termination *(n, %)*		
Adverse event	7 (20.6 %)	3 (8.1 %)
Withdrawal of consent	1 (2.9 %)	1 (2.7 %)
Incompliance	0	2 (5.4 %)
Violation study drug dose	1 (2.9 %)	0
Investigator judgement	1 (2.9 %)	4 (10.8 %)
Other	1 (2.9 %)	1 (2.7 %)

Table 7: IMP-intake discontinuation.

Premature termination of study: 23/71 patients discontinued study participation prematurely (before visit 13). The reasons for early study discontinuation for patients in the ITT set are given in table 8 (multiple reasons were acceptable).

	Treatment group	
	Clozapine (N = 34)	Olanzapine (N = 37)
Premature termination of study (before V13) *(n, %)*	11 (32.4 %)	12 (32.4 %)
Reason for premature termination of study *(n, %)*		
Participation in further study visits rejected	2 (5.9 %)	3 (8.1 %)
Withdrawal of consent	1 (2.9 %)	1 (2.7 %)
No ability to give consent	0	1 (2.7 %)
Lost to follow up	2 (5.9 %)	3 (8.1 %)
Death	0	0
Other	6 (17.6 %)	5 (13.5 %)

Table 8: Study discontinuation.

Safety Assessments (all patients included)

Annual Safety Reports have been provided to BfArM and EC for the following periods:
DSUR 1: 17.06.2019- 09.12.2019
DSUR 2: 10.12.2020- 09.12.2020
DSUR 3: 10.12.2020- 09.12.2021
DSUR 4: 10.12.2021- 09.12.2022
DSUR 5: 10.12.2022- 09.12.2023
DSUR 6: 10.12.2023- 09.12.2024
Adverse Events and Serious Adverse Events were classified according to CTCAE v4.03; and MedDRA Version 20.0. English.

Safety Results

Safety results are reported in the treatment groups of the actual study treatment, regardless of randomization.

Adverse Events (AE)

A total of 585 AEs in 71 patients were reported during the study, 345 in the clozapine group and 240 in the olanzapine group. The most common AEs (incidence ≥ 5 %) are summarized in Supplementary Table 1. Table 9 shows further details regarding the AEs. The relatedness of AEs was more likely in group 1 (clozapine). Most AEs were rated as mild and recovered/resolved in both study groups.

	Treatment group	
	Clozapine (N* = 345)	Olanzapine (N* = 240)
Relationship *(n, %)*		
highly probable/definite	37 (10.7 %)	12 (5.0 %)
probably related	74 (21.5 %)	51 (21.3 %)
possibly related	131 (38.0 %)	76 (31.7 %)
unlikely	88 (25.5 %)	74 (30.8 %)
not related	15 (4.4 %)	27 (11.3 %)
Severity *(n, %)*		
mild	310 (89.9 %)	206 (85.8 %)
moderate	19 (5.5 %)	30 (12.5 %)
severe	16 (4.6 %)	3 (1.3 %)
life-threatening	0	1 (0.4 %)
Outcome *(n, %)*		
not recovered/not resolved/unchanged	66 (19.1 %)	47 (19.6 %)
recovered/resolved	263 (76.2 %)	186 (77.5 %)
improving/recovering/resolving	8 (2.3 %)	3 (1.3 %)
recovered with sequelae	1 (0.3 %)	1 (0.4 %)
unknown	7 (2.0 %)	3 (1.3 %)

* number of AEs (not patients)

Table 9: AE relatedness, intensity, and outcome

34/35 (97.1 %) patients experienced 345 AEs in group 1 (clozapine), 37/39 (94.9 %) patients experienced 240 AEs in group 2 (olanzapine). The overall incidence of AEs did not differ between treatment groups, however some types of expected AEs appeared more often in one group than the other. This disbalance is due to the nature of the IMPs and is entirely in line with the current list of possible AEs. Supplementary Table 1 contains the p-values from the group comparisons by MedDRA System Organ Class and overall.

Serious AE (SAE)

20 SAE were reported in eleven patients; 15 SAEs in 7/35 (20.0 %) patients in Group 1 (Clozapine) and 5 in 4/39 (10.3 %) patients in Group 2 (Olanzapine).

Suspected Serious Adverse Reactions (SAR)

10 SAEs in the clozapine group and 1 SAE in the olanzapine group were defined as related. The outcome for all SAEs was “recovered/resolved”.

Suspected Unexpected Serious Adverse Reactions (SUSAR)

No SUSAR was reported.

Non-serious Adverse Events (AE)

A total of 565 non-serious AE in 70 (95.6 %) patients were reported during the study. 330 non-serious AEs in 34/35 (97.1%) patients in group 1 (clozapine) and 235 non-serious AEs in 36/39 (92.3 %) patients in group 2 (olanzapine).

Efficacy Results

Primary Endpoint

No difference between the two treatment arms could be shown. This result was robust against alterations in the analysis set and the type of missing-value-imputation. Table 10 shows a summary of the statistical analysis of the primary endpoint. Table 11 gives descriptive statistics of the primary endpoint within the different analysis sets.

Remission at week 8 ***(n, %)***	**OR**	**95%CI**	**p-value**
Primary analysis *(ITT, conservative imputation)*	1.20	(0.47, 3.06)	0.702
Additional analyses of the primary endpoint			
Complete case analysis *(ITT, complete case)*	0.78	(0.29, 2.09)	0.614
Missing PANSS imputed as non-remitters *(ITT, different imputation)*	0.69	(0.26, 1.78)	0.439
Per-protocol analysis *(PP)*	0.68	(0.23, 2.01)	0.487
Logistic regression* *(ITT, conservative imputation)*			0.148
Treatment group (clozapine vs. olanzapine) for patients with one previous treatment	0.22	(0.03, 1.71)	
Treatment group (clozapine vs. olanzapine) for patients with more than one previous treatment	1.25	(0.42, 3.68)	

* Model including treatment group (clozapine vs. olanzapine), number previous treatments (>1 vs. 1), and their interaction. The p-value of the Wald Chi-square statistic for treatment group and the OR within the groups of no. prev. treatments are reported.

Table 10: Primary endpoint (remission at week 8)

Remission at week 8 *(n, %)*	Treatment group			
	Clozapine		Olanzapine	
	N	n %	N	n %
Primary analysis *(ITT, conservative imputation)*	34	15 (44.1 %)	37	18 (48.7 %)
Complete case analysis *(ITT, complete case)*	32	15 (46.9 %)	32	13 (40.6 %)
Missing PANSS imputed as non-remitters *(ITT, different imputation)*	34	15 (44.1 %)	37	13 (35.1 %)
Per-protocol analysis *(PP)*	25	14 (56.0 %)	28	13 (46.4 %)

Table 11: Number of remitters at week 8 per treatment group using different analysis sets and imputation techniques.

Secondary Endpoints

The secondary efficacy endpoints were analyzed both on the ITT and the PP set. The observed differences between treatment groups were not statistically significant. The results are summarized in tables 12 (ITT) and 13 (PP).

ITT set		Treatment group			p-value
		Clozapine		Olanzapine	
		n %		n %	
	N	*median range*	N	*median range*	
Remission at week 4 *(n, %)*	25	5 (20.0 %)	30	10 (33.3 %)	0.269
Change in total PANSS from BL to					
Week 4	25	*-17 (-96 – 0)*	30	*-16.5 (-53 – 12)*	0.450*
Week 8	31	*-26 (-109 – 7)*	32	*-19 (-63 – 21)*	0.493*
Change in positive PANSS from BL to					
Week 4	25	*-7 (-22 – 1)*	30	*-6 (-14 – 2)*	0.727*
Week 8	31	*-8 (-25 – 3)*	32	*-7.5 (-14 – 10)*	0.366*
Change in negative PANSS from BL to					
Week 4	25	*-4 (-14 – 3)*	30	*-2 (-12 – 5)*	0.507*
Week 8	31	*-5 (-13 – 6)*	32	*-2.5 (-16 – 4)*	0.718*
Change in general PANSS from BL to					
Week 4	25	*-8 (-73 – 3)*	30	*-7.5 (-30 – 11)*	0.419*
Week 8	31	*-12 (-80 – 8)*	32	*-11 (-34 – 8)*	0.629*
Remission w/out negative symptoms					
Week 4	25	9 (36.0 %)	30	17 (56.7 %)	0.126
Week 6	26	17 (65.4 %)	27	16 (59.3 %)	0.646
Week 8	32	22 (68.8 %)	32	18 (56.3 %)	0.302
Clinical response					
Week 4	25	20 (80.0 %9	30	18 (60.0 %)	0.110
Week 8	31	25 (80.7 %)	32	24 (75.0 %)	0.590

Baseline=BL (V1); week 1 (V2); week 2 (V3); week 3 (V4); week 4 (V5); week 5 (V6); week 6 (V7); week 7 (V8); week 8 (V9);
** p-value for treatment group from a linear regression model including treatment group and baseline value as covariates*

Table 12: Secondary endpoint results on the ITT set

PP set	Treatment group				p-value
		Clozapine n %		Olanzapine n %	
	N	*median range*	N	*median range*	
Remission at week 4 *(n, %)*	24	5 (20.8 %)	28	10 (35.7 %)	0.238
Change in total PANSS from BL to					
Week 4	24	*-17 (-96 – 0)*	28	*-17.5 (-53 – 12)*	0.477*
Week 8	25	*-26 (-109 – 7)*	28	*-22 (-63 – 5)*	0.704*
Change in positive PANSS from BL to					
Week 4	24	*-7 (-22 – 1)*	28	*-6.5 (-14 – 2)*	0.855*
Week 8	25	*-8 (-25 – 0)*	28	*-8 (-14 – 1)*	0.471*
Change in negative PANSS from BL to					
Week 4	24	*-4 (-14 – 3)*	28	*-2 (-12 – 5)*	0.533*
Week 8	25	*-5 (-13 – 0)*	28	*-3.5 (-16 – 4)*	0.813*
Change in general PANSS from BL to					
Week 4	24	*-8 (-73 – 3)*	28	*-8 (-30 – 11)*	0.456*
Week 8	25	*-12 (-80 – 8)*	28	*-11 (-34 – 5)*	0.901*
Remission w/out negative symptoms					
Week 4	24	9 (37.5 %)	28	17 (60.7 %)	0.095*
Week 6	25	17 (68.0 %)	27	16 (59.3 %)	0.513*
Week 8	25	18 (72.0 %)	28	18 (64.3 %)	0.548*
Clinical response					
Week 4	24	20 (83.3 %)	28	18 (64.3 %)	0.123*
Week 8	25	21 (84.0 %)	28	23 (82.1 %)	0.857*

Baseline=BL (V1); week 1 (V2); week 2 (V3); week 3 (V4); week 4 (V5); week 5 (V6); week 6 (V7); week 7 (V8); week 8 (V9);
** p-value for treatment group from a linear regression model including treatment group and baseline value as covariates*

Table 13: Secondary endpoint results on the PP set

Several safety endpoints were analyzed on the safety set. Treatment group differences were seen for changes from baseline to various time points for lymphocytes, heart rate, and QT time. Details are shown in supplementary tables 3 – 15.
Assessments listed under “other clinical assessments” were compared at major visits. The differences observed were not statistically significant. This analysis was done on the ITT set. Detailed results can be seen in supplementary table 16.
Assessments listed under “other safety assessments” were analyzed on the safety set. Available values were compared visit-based between treatment arms. Some statistically significant differences were seen in blood pressure and heart rate. Detailed results can be seen in supplementary table 17.

Overall Conclusion

Achieving symptomatic remission quickly after the onset of psychotic symptoms is the critical objective in schizophrenia treatment and determines the subsequent disease. course. In this context, only every second patient with acute schizophrenia achieves symptomatic remission within three months of initiating antipsychotic treatment, meaning that half of patients do not achieve this key objective. Increasing the likelihood to achieve symptomatic remission in acute schizophrenia will improve the overall outcome, reduce disease-associated burden and potentially prevent mid- and long-term disease chronicity. With this randomized, double-blind, parallel-group multicentre trial we aimed to provide evidence for the superior efficacy of the ‘last resort’ antipsychotic clozapine compared to one of the most effective second-generation antipsychotics (SGAs), olanzapine, in acute schizophrenia patients who do not meet the criteria for treatment-naive or treatment-resistant schizophrenia. We conducted a double-blind, eight-week treatment with either clozapine or olanzapine and the primary endpoint was the number of patients in symptomatic remission at the end of week eight according to the

	international consensus criteria for remission. We planned to randomize a total of 220 patients, but due to problems in achieving the recruitment rates in some centres and significant delays due to the COVID19 pandemic, we were unable to reach this recruitment goal. However, some centers showed that recruitment rates as expected were possible highlighting that no design aspects hampered recruitment. In the end, 75 patients were included in the study of which 71 patients could be analysed. No unexpected side-effects occurred. We assumed that patients who received clozapine will show a higher frequency of remission compared to those who received olanzapine. However, the primary endpoint analyses showed no significant distribution in remission rates between both study groups. Thus, the trial is negative, and we could not confirm our primary study hypothesis. Following our findings, the idea to provide a clozapine treatment prior to the stage of treatment-resistance must be questioned. The question of whether clozapine should be offered as a second-line option is still topical and the results of our study come at exactly the right time. In a population-based study from Finland published in 2025, there was evidence that clozapine appears to be more effective in people with a first episode of schizophrenia and failure of antipsychotic treatment (Taipale, Tanskanen et al. 2025; Lancet Psychiatry 2(2):122-130). The journal Lancet Psychiatry has published an editorial with the title “Should clozapine be offered as a second-line antipsychotic?” to accompany the cited study by Taipale et al., where the following conclusion can be found: "Even if an RCT were to provide evidence for offering clozapine early, what would need to happen for this to translate into clinical practice? This question was poignantly ad-dressed in statements given to the US Food and Drug Administration by families of people taking clozapine, who made the case for clozapine being offered more widely, in line with re-consideration of monitoring. The committee voted in favour of this, thereby facilitating clozapine prescribing. If RCTs indicate benefit, the issue for the field will be implementation, address-ing legitimate concerns about side-effects through better monitoring and adjunctive treatment, and how benefits and risks of clozapine are conveyed to clinicians, patients, and their families." (Butler, Stratford et al. 2025; 12(2):85-86.). EARLY is, as detailed above, negative at the primary endpoint, but offers the potential to complement many analyses to answer this clinically very relevant question, which is very relevant at the beginning of the study and is still very relevant today. Our finding that there was a clinically relevant and significant improvement in psychopathology in both groups at low doses and serum levels seems important. This once again underlines the high efficacy of both investigational substances and the need in clinical practice to adhere to minimally effective dosages in accordance with the AWMF-S3 guideline. Despite the low dosages, a relevant number of AEs occurred – the only relevant difference between the two test substances relates primarily to the cardiac side effects.
21.	**Date of report:** **Date:** 25.01.2026 **Signature:** _____ SDP: Prof. Dr. med. Alkomiet. Hasan

APPENDIX

Supplementary Figure 1 CONSORT Chart

Supplementary Table 1 All AEs

Supplementary Table 2 All SAEs

Supplementary Table 3 Change in WBC (G/L) from Baseline (Safety Set)

Supplementary Table 4 Change in Neutrophils abs. (G/L) from Baseline (Safety Set)

Supplementary Table 5 Change in Lymphocytes (G/L) from Baseline (Safety Set)

Supplementary Table 6 Change in Monocytes (G/L) from Baseline (Safety Set)

Supplementary Table 7 Change in Eosinophils (G/L) from Baseline (Safety Set)

Supplementary Table 8 Change in Eosinophils (G/L) from Baseline (Safety Set)

Supplementary Table 8 Change in Erythrocytes (G/L) from Baseline (Safety Set)

Supplementary Table 9 Change in Thrombocytes (G/L) from Baseline (Safety Set)

Supplementary Table 10 Change in CK total (G/L) from Baseline (Safety Set)

Supplementary Table 11 Change in CRP (mg/dl) from Baseline (Safety Set)

Supplementary Table 12 Change in Troponin (ng/dl) from Baseline (Safety Set)

Supplementary Table 13 Two-fold Elevated Troponin (Safety Set)

Supplementary Table 14 Change in Heart Rate from Baseline (Safety Set)

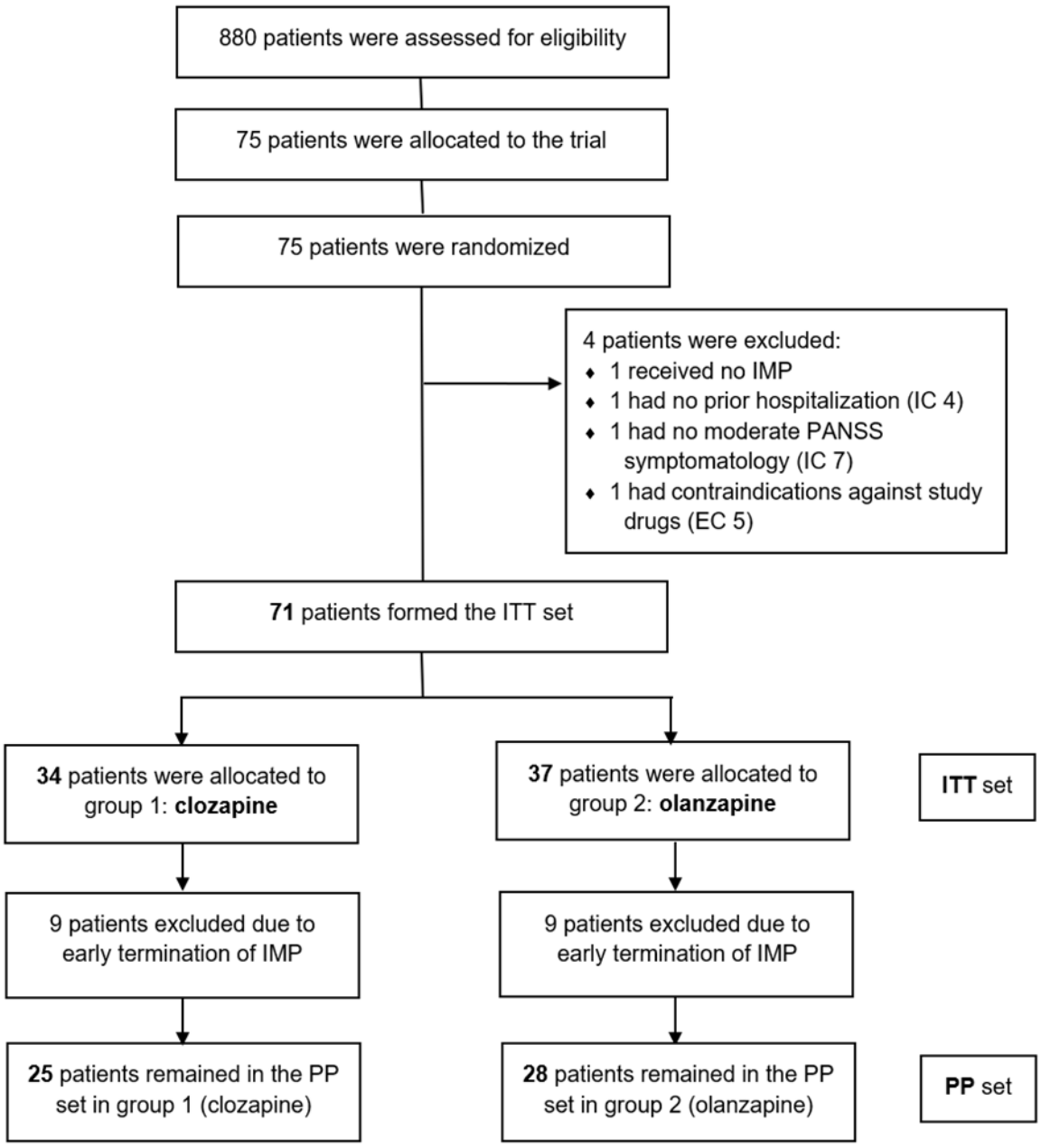
Supplementary Table 15 Change in QT Time from Baseline (Safety Set)

Supplementary Table 16 Other clinical assessments (ITT)

Supplementary Table 17 Other safety assessments (safety set)

Supplementary Table 18 IP Blood Levels (ug/L)

Supplementary Figure 1: CONSORT Chart



Supplementary Table 1 All AEs
Preferred terms are presented only if their incidence was ≥ 5% per treatment group.

System Organ Class Preferred Term	Exposed to clozapine N=35			Exposed to olanzapine N=39			p-value
		Subjects affected			Subjects affected		
	Events	n	(%)	Events	n	(%)	
OVERALL	**345**	**34**	**(97)**	**240**	**37**	**(95)**	1.000
Blood and lymphatic system disorders	**24**	**6**	**(17)**	**22**	**7**	**(18)**	1.000
Eosinophilia	4	3	(9)	0	0	(0)	
Leukocytosis	4	3	(9)	8	4	(10)	
Lymphopenia	3	2	(6)	0	0	(0)	
Neutropenia	2	1	(3)	2	2	(5)	
Neutrophilia	3	2	(6)	5	2	(5)	
Thrombocytopenia	2	2	(6)	0	0	(0)	
Cardiac disorders	**20**	**15**	**(43)**	**2**	**2**	**(5)**	< 0.001
Myocarditis	3	3	(9)	0	0	(0)	
Sinus tachycardia	3	3	(9)	0	0	(0)	
Tachycardia	13	12	(34)	1	1	(3)	
Ear and labyrinth disorders	**7**	**7**	**(20)**	**4**	**2**	**(5)**	0.075
Vertigo	7	7	(20)	3	2	(5)	
Eye disorders	**5**	**5**	**(14)**	**2**	**2**	**(5)**	0.245
Vision blurred	4	4	(11)	2	2	(5)	
Gastrointestinal disorders	**71**	**27**	**(77)**	**32**	**20**	**(51)**	0.030
Abdominal pain	1	1	(3)	2	2	(5)	
Abdominal pain upper	1	1	(3)	2	2	(5)	
Abdominal tenderness	1	1	(3)	1	1	(3)	
Constipation	15	11	(31)	7	7	(18)	
Diarrhoea	5	4	(11)	4	4	(10)	
Dyspepsia	3	3	(9)	1	1	(3)	
Gastrooesophageal reflux disease	6	5	(14)	0	0	(0)	
Nausea	12	9	(26)	2	2	(5)	
Salivary hypersecretion	21	20	(57)	4	4	(10)	
Toothache	0	0	(0)	4	2	(5)	
Vomiting	4	4	(11)	1	1	(3)	
General disorders and administration site conditions	**27**	**20**	**(57)**	**19**	**12**	**(31)**	0.057
Asthenia	6	6	(17)	2	2	(5)	
Fatigue	11	9	(26)	12	9	(23)	
General physical health deterioration	2	2	(6)	0	0	(0)	
Pyrexia	5	5	(14)	0	0	(0)	
Thirst	2	2	(6)	0	0	(0)	
Infections and infestations	**3**	**3**	**(9)**	**4**	**4**	**(10)**	1.000
Injury, poisoning and procedural complications	**1**	**1**	**(3)**	**2**	**2**	**(5)**	1.000
Investigations	**63**	**25**	**(71)**	**48**	**26**	**(67)**	0.802
Alanine aminotransferase increased	7	7	(20)	2	2	(5)	
Aspartate aminotransferase increased	4	4	(11)	3	2	(5)	
Blood creatine phosphokinase increased	6	4	(11)	6	5	(13)	
C-reactive protein increased	10	9	(26)	6	5	(13)	
Drug level above therapeutic	2	2	(6)	0	0	(0)	
Electroencephalogram abnormal	2	2	(6)	0	0	(0)	
Eosinophil count increased	0	0	(0)	2	2	(5)	
Gamma-glutamyltransferase increased	0	0	(0)	2	2	(5)	
High density lipoprotein decreased	2	2	(6)	0	0	(0)	
Neutrophil count decreased	2	1	(3)	2	2	(5)	
Transaminases increased	6	5	(14)	5	4	(10)	
Troponin increased	5	4	(11)	0	0	(0)	
Weight increased	4	4	(11)	11	11	(28)	
White blood cell count decreased	2	2	(6)	3	2	(5)	
Metabolism and nutrition disorders	**20**	**17**	**(49)**	**18**	**14**	**(36)**	0.347

System Organ Class Preferred Term	Exposed to clozapine N=35			Exposed to olanzapine N=39			p-value
	Events	Subjects affected n	(%)	Events	Subjects affected n	(%)	
Folate deficiency	2	2	(6)	0	0	(0)	
Hyperglycaemia	2	2	(6)	0	0	(0)	
Hypertriglyceridaemia	4	4	(11)	5	4	(10)	
Increased appetite	10	9	(26)	10	10	(26)	
Musculoskeletal and connective tissue disorders	**3**	**3**	**(9)**	**14**	**11**	**(28)**	0.040
Back pain	1	1	(3)	2	2	(5)	
Myalgia	0	0	(0)	2	2	(5)	
Pain in extremity	0	0	(0)	5	4	(10)	
Nervous system disorders	**32**	**20**	**(57)**	**27**	**16**	**(41)**	0.244
Akathisia	0	0	(0)	2	2	(5)	
Dizziness	2	2	(6)	1	1	(3)	
Headache	6	6	(17)	5	5	(13)	
Hypoaesthesia	0	0	(0)	2	2	(5)	
Hypotonia	2	2	(6)	0	0	(0)	
Somnolence	14	14	(40)	7	7	(18)	
Tremor	1	1	(3)	3	3	(8)	
Psychiatric disorders	**30**	**18**	**(51)**	**24**	**10**	**(26)**	0.031
Anxiety	2	2	(6)	3	2	(5)	
Depressed mood	4	4	(11)	3	3	(8)	
Enuresis	10	7	(20)	0	0	(0)	
Insomnia	1	1	(3)	2	2	(5)	
Restlessness	4	4	(11)	3	2	(5)	
Sleep disorder	4	4	(11)	4	4	(10)	
Suicidal ideation	0	0	(0)	3	3	(8)	
Renal and urinary disorders	**13**	**7**	**(20)**	**5**	**5**	**(13)**	0.531
Cystitis noninfective	0	0	(0)	1	1	(3)	
Pollakiuria	4	3	(9)	2	2	(5)	
Urinary incontinence	5	3	(9)	0	0	(0)	
Reproductive system and breast disorders	**2**	**2**	**(6)**	**1**	**1**	**(3)**	0.600
Respiratory, thoracic and mediastinal disorders	**16**	**11**	**(31)**	**9**	**6**	**(15)**	0.166
Cough	7	6	(17)	2	2	(5)	
Epistaxis	1	1	(3)	3	2	(5)	
Oropharyngeal pain	4	4	(11)	1	1	(3)	
Rhinorrhoea	2	2	(6)	0	0	(0)	
Skin and subcutaneous tissue disorders	**6**	**5**	**(14)**	**2**	**2**	**(5)**	0.245
Dry skin	2	2	(6)	1	1	(3)	
Hyperhidrosis	3	2	(6)	0	0	(0)	
Vascular disorders	**2**	**2**	**(6)**	**4**	**4**	**(10)**	0.677
Hypertension	1	1	(3)	2	2	(5)	
Hypotension	1	1	(3)	2	2	(5)	

Supplementary Table 2 All SAEs

System Organ Class Preferred Term	Exposed to clozapine N=35		Exposed to olanzapine N=39		p-value
	Events	Subjects affected n (%)	Events	Subjects affected n (%)	
OVERALL	**15**	**7 (20)**	**5**	**4 (10)**	0.333
Blood and lymphatic system disorders	**1**	**1 (3)**	**0**	**0 (0)**	0.473
Neutropenia	1	1 (3)	0	0 (0)	
Cardiac disorders	**4**	**4 (11)**	**1**	**1 (3)**	0.183
Myocardial infarction	0	0 (0)	1	1 (3)	
Myocarditis	3	3 (9)	0	0 (0)	
Tachycardia	1	1 (3)	0	0 (0)	
Gastrointestinal disorders	**1**	**1 (3)**	**0**	**0 (0)**	0.473
Diarrhoea	1	1 (3)	0	0 (0)	
General disorders and administration site conditions	**3**	**2 (6)**	**0**	**0 (0)**	0.220
General physical health deterioration	1	1 (3)	0	0 (0)	
Pyrexia	2	2 (6)	0	0 (0)	
Infections and infestations	**1**	**1 (3)**	**0**	**0 (0)**	0.473
Sepsis syndrome	1	1 (3)	0	0 (0)	
Injury, poisoning and procedural complications	**1**	**1 (3)**	**1**	**1 (3)**	1.000
Overdose	1	1 (3)	0	0 (0)	
Toxicity to various agents	0	0 (0)	1	1 (3)	
Investigations	**2**	**2 (6)**	**1**	**1 (3)**	0.600
Troponin I increased	0	0 (0)	1	1 (3)	
Troponin T increased	1	1 (3)	0	0 (0)	
Troponin increased	1	1 (3)	0	0 (0)	
Psychiatric disorders	**2**	**1 (3)**	**2**	**2 (5)**	1.000
Drug use disorder	1	1 (3)	0	0 (0)	
Psychotic disorder	1	1 (3)	1	1 (3)	
Suicidal ideation	0	0 (0)	1	1 (3)	

Supplementary Table 3 Change in WBC (G/L) from Baseline (Safety Set)

		Treatment group										
		Clozapine					*Olanzapine*					
		Change in WBC					*Change in WBC*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-2.70	-0.48	0.17	1.10	3.82	38	-1.88	-0.63	0.20	1.03	6.60	0.8879
V3	33	-1.70	-0.40	0.78	2.17	5.99	37	-8.60	-0.90	0.10	1.50	5.43	0.0995
V4	31	-3.60	-0.16	0.92	1.80	5.12	35	-5.40	-0.45	0.10	1.00	3.41	0.1097
V5	30	-2.81	-0.30	1.01	2.05	5.19	34	-3.57	-0.83	0.15	1.15	3.00	0.0415
V6	31	-4.00	-0.61	0.55	1.10	5.17	32	-2.21	-0.16	0.22	1.69	11.57	0.8420
V7	29	-5.60	-0.41	0.20	0.90	3.41	32	-3.31	-0.90	-0.15	0.69	3.50	0.4702
V8	26	-3.14	-1.14	-0.31	0.81	7.36	29	-3.04	-0.87	0.00	1.00	7.73	0.6982
V9	29	-3.80	-0.90	0.05	0.80	4.06	32	-3.05	-0.79	0.13	1.01	6.13	0.6753
V10	26	-4.20	-0.91	0.40	1.70	6.46	28	-3.23	-0.59	0.20	0.86	4.20	0.5737
V11	24	-2.80	-0.27	0.23	1.98	4.16	29	-3.69	-0.75	0.05	1.25	6.90	0.4971
V12	24	-3.16	-0.66	0.57	1.83	7.30	29	-3.76	-0.93	0.30	1.47	3.70	0.3812
V13	23	-4.90	-1.26	0.23	2.06	3.87	25	-3.04	-0.60	0.10	1.26	5.53	0.9753

Supplementary Table 4 Change in Neutrophyls abs. (G/L) from Baseline (Safety Set)

		Treatment group										
		Clozapine					*Olanzapine*					
		Change in Neutrophyls (abs.)					*Change in Neutrophyls (abs.)*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-2.56	-0.21	0.12	0.89	4.48	37	-2.02	-0.47	0.28	0.84	6.20	0.9175
V3	32	-1.69	-0.14	0.28	1.88	5.81	36	-7.16	-0.60	-0.13	1.01	4.61	0.0340
V4	31	-4.43	-0.03	0.80	1.35	4.85	34	-4.72	-0.55	0.10	0.70	3.18	0.0466
V5	30	-2.70	-0.22	0.71	1.51	4.71	33	-3.52	-0.84	-0.08	0.84	2.27	0.0282
V6	31	-4.40	-0.48	0.02	0.94	5.09	31	-1.95	-0.67	0.17	0.99	10.79	0.7945
V7	29	-5.47	-0.49	0.01	0.44	3.53	30	-2.22	-0.68	-0.02	0.51	2.93	0.8201
V8	26	-2.50	-0.74	-0.26	0.71	8.09	28	-2.58	-0.72	-0.16	0.55	5.86	0.9655
V9	28	-3.80	-0.53	0.11	0.76	4.87	31	-2.59	-0.64	0.01	1.15	4.76	0.8140
V10	25	-3.95	-0.33	0.56	1.28	7.69	26	-2.97	-0.85	0.16	0.66	3.75	0.2315
V11	24	-2.33	-0.37	0.44	1.98	5.04	28	-3.18	-0.93	-0.08	1.00	6.78	0.1209
V12	23	-1.53	-0.06	0.62	1.73	7.61	28	-3.25	-0.73	0.29	1.03	3.67	0.1206
V13	23	-4.27	-0.51	-0.15	2.22	4.12	25	-2.79	-0.77	0.02	0.74	5.00	0.5024

Supplementary Table 5 Change in Lymphocytes (G/L) from Baseline (Safety Set)

		Treatment group											
		Clozapine					*Olanzapine*						
		Change in Lymphocytes					*Change in Lymphocytes*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-38.49	-0.42	-0.21	0.13	0.69	36	-1.23	-0.20	-0.04	0.29	1.46	0.0800
V3	32	-40.38	-0.46	-0.29	0.12	1.33	36	-0.90	-0.23	0.15	0.41	1.12	0.0108
V4	31	-40.95	-0.42	-0.11	0.21	0.77	34	-1.25	-0.04	0.14	0.32	1.34	0.0297
V5	30	-39.49	-0.57	-0.12	0.28	0.72	33	-1.64	-0.21	0.16	0.34	0.85	0.1001
V6	31	-40.13	-0.43	-0.00	0.29	0.53	31	-0.80	-0.15	0.21	0.55	0.97	0.0120
V7	29	-40.39	-0.43	-0.08	0.10	1.05	31	-4.41	-0.34	0.01	0.33	1.17	0.3363
V8	26	-40.66	-0.51	-0.25	0.00	0.71	28	-1.23	-0.15	0.14	0.45	1.26	0.0044
V9	28	-41.19	-0.74	-0.31	0.02	0.51	31	-0.78	-0.21	0.09	0.47	0.91	0.0018
V10	25	-40.68	-0.65	-0.17	0.06	0.93	27	-1.68	-0.15	0.12	0.43	1.02	0.0402
V11	24	-40.82	-0.65	-0.38	0.04	0.70	28	-4.04	-0.24	0.25	0.55	1.38	0.0044
V12	23	-41.27	-0.54	-0.18	0.08	1.24	28	-1.97	-0.00	0.17	0.56	1.55	0.0059
V13	23	-40.76	-0.77	-0.35	-0.03	1.03	25	-2.14	-0.13	0.13	0.50	1.73	0.0026

Supplementary Table 6 Change in Monocytes (G/L) from Baseline (Safety Set)

		Treatment group											
		Clozapine					*Olanzapine*						
		Change in Monocytes					*Change in Monocytes*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-0.28	-0.01	0.04	0.10	0.60	36	-0.24	-0.09	-0.01	0.09	0.43	0.1208
V3	32	-0.10	0.01	0.13	0.19	0.58	36	-0.42	-0.10	-0.04	0.09	0.72	0.0003
V4	31	-0.20	-0.02	0.07	0.15	0.37	34	-0.27	-0.08	0.01	0.06	0.63	0.0940
V5	30	-0.21	-0.05	0.02	0.14	0.34	33	-0.32	-0.03	0.01	0.09	0.26	0.5679
V6	31	-0.19	-0.04	0.03	0.13	0.43	31	-0.36	-0.05	0.05	0.19	0.39	0.5172
V7	29	-0.26	-0.04	0.03	0.18	0.44	31	-0.38	-0.07	0.01	0.09	0.26	0.2485
V8	26	-0.17	-0.08	0.05	0.17	0.44	28	-0.45	-0.04	0.07	0.12	0.68	0.9035
V9	28	-0.25	-0.04	0.04	0.13	0.23	31	-0.40	-0.08	0.04	0.14	0.41	0.9576
V10	25	-0.26	-0.07	0.04	0.13	0.54	27	-0.39	-0.12	0.01	0.10	0.32	0.4203
V11	24	-0.26	-0.14	0.06	0.12	0.37	28	-0.43	-0.09	0.00	0.19	0.54	0.9780
V12	23	-0.23	-0.02	0.06	0.18	0.52	28	-0.44	-0.07	0.02	0.15	0.35	0.4048
V13	23	-0.22	-0.07	0.04	0.14	0.40	25	-0.29	-0.10	0.00	0.09	0.29	0.2117

Supplementary Table 7 Change in Eosinophils (G/L) from Baseline (Safety Set)

	Treatment group											
	Clozapine						*Olanzapine*					
	Change in Eosinophils						*Change in Eosinophils*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-0.51	-0.02	-0.00	0.04	0.13	36	-0.08	-0.00	0.01	0.08	0.29	0.0927
V3	32	-0.54	0.02	0.05	0.11	0.24	36	-0.29	-0.01	0.04	0.06	0.58	0.2850
V4	31	-0.34	0.00	0.10	0.21	0.62	34	-0.15	0.00	0.05	0.07	0.37	0.0560
V5	30	-0.59	-0.01	0.08	0.28	1.76	33	-0.08	-0.02	0.05	0.13	0.35	0.2562
V6	31	-0.71	0.02	0.09	0.22	0.66	31	-0.09	0.00	0.05	0.15	0.45	0.1490
V7	29	-0.63	0.00	0.09	0.18	0.64	31	-0.20	-0.03	0.04	0.11	0.32	0.0875
V8	26	-0.65	-0.00	0.05	0.11	0.38	28	-0.17	-0.02	0.03	0.13	0.33	0.6651
V9	28	-0.67	-0.03	0.01	0.10	0.18	31	-0.26	-0.02	0.02	0.10	0.38	0.6379
V10	25	-0.69	-0.06	-0.01	0.04	0.16	27	-0.26	-0.05	0.03	0.10	0.34	0.2677
V11	24	-0.75	-0.07	-0.02	0.03	0.15	28	-0.25	-0.02	0.01	0.08	0.34	0.0912
V12	23	-0.76	-0.07	-0.03	0.08	0.20	28	-0.25	-0.02	0.02	0.10	0.28	0.0546
V13	23	-0.74	-0.07	0.00	0.03	0.15	25	-0.23	0.00	0.06	0.10	0.35	0.0192

Supplementary Table 8 Change in Eosinophils (G/L) from Baseline (Safety Set)

	Treatment group											
	Clozapine						*Olanzapine*					
	Change in Basophils						*Change in Basophils*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-0.03	-0.01	0.00	0.01	0.03	36	-0.05	-0.01	0.00	0.01	0.06	0.5317
V3	32	-0.06	-0.02	0.00	0.01	0.05	36	-0.10	-0.01	0.00	0.01	0.06	0.2368
V4	31	-0.06	-0.01	0.01	0.02	0.07	34	-0.09	-0.02	0.00	0.02	0.05	0.1717
V5	30	-0.04	0.00	0.01	0.04	0.07	33	-0.04	-0.01	0.00	0.01	0.06	0.0081
V6	31	-0.04	-0.01	0.01	0.03	0.05	31	-0.03	-0.01	0.00	0.02	0.06	0.2569
V7	29	-0.04	-0.01	0.00	0.02	0.04	31	-0.05	-0.01	-0.00	0.01	0.07	0.1304
V8	26	-0.03	-0.01	0.01	0.02	0.04	28	-0.03	-0.01	0.00	0.02	0.34	0.6459
V9	28	-0.02	-0.00	0.00	0.01	0.04	31	-0.04	-0.01	0.00	0.01	0.08	0.4937
V10	25	-0.03	-0.01	0.01	0.01	0.06	27	-0.06	-0.01	0.00	0.01	0.06	0.2370
V11	24	-0.04	-0.01	0.00	0.01	0.05	28	-0.07	-0.01	0.00	0.01	0.04	0.9559
V12	23	-0.06	-0.01	0.00	0.02	0.04	28	-0.04	-0.01	0.00	0.01	0.04	0.2507
V13	23	-0.03	-0.01	0.00	0.02	0.06	25	-0.06	-0.01	0.00	0.01	0.04	0.7479

Supplementary Table 8 Change in Erythrozyten (G/L) from Baseline (Safety Set)

	Treatment group											
	Clozapine					*Olanzapine*						
	Change in Erythrozyten					*Change in Erythrozyten*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-0.41	-0.12	0.04	0.19	0.58	38	-0.59	-0.11	0.04	0.21	0.40	0.8923
V3	33	-0.70	-0.16	0.01	0.15	0.40	37	-0.63	-0.10	0.04	0.14	0.61	0.6170
V4	31	-0.73	-0.21	0.05	0.19	0.52	35	-0.66	-0.15	-0.01	0.13	0.56	0.6951
V5	30	-0.81	-0.19	0.01	0.19	0.37	34	-0.85	-0.23	-0.01	0.18	0.59	0.7982
V6	31	-0.66	-0.32	-0.11	0.22	0.58	32	-0.76	-0.22	-0.04	0.13	0.46	0.7414
V7	29	-0.93	-0.29	-0.02	0.14	0.73	32	-0.73	-0.27	-0.02	0.15	0.37	0.9080
V8	26	-0.84	-0.40	-0.04	0.18	0.66	29	-0.70	-0.22	0.05	0.22	0.43	0.3494
V9	29	-0.86	-0.17	0.01	0.18	0.72	32	-0.57	-0.12	0.03	0.19	0.61	0.7343
V10	26	-0.83	-0.39	-0.04	0.09	0.76	28	-0.60	-0.15	0.03	0.23	0.57	0.2062
V11	24	-0.80	-0.44	-0.06	0.12	0.89	29	-0.60	-0.22	-0.03	0.11	0.54	0.3811
V12	24	-0.91	-0.36	-0.10	0.23	0.79	29	-0.52	-0.18	0.06	0.19	0.50	0.3620
V13	23	-0.73	-0.27	-0.07	0.13	0.90	26	-0.58	-0.20	0.01	0.24	0.58	0.5020

Supplementary Table 9 Change in Thrombozyten (G/L) from Baseline (Safety Set)

	Treatment group											
	Clozapine					*Olanzapine*						
	Change in Thrombozyten					*Change in Thrombozyten*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-63	-12	-1.5	13	52	38	-74	-20	0.5	20	161	0.7054
V3	33	-73	-2	11	40	126	37	-68	-21	11	21	148	0.2738
V4	31	-40	12	32	64	251	35	-87	-24	-1	22	169	0.0022
V5	30	-75	3	32.5	47	134	34	-87	-14	-2.5	16	150	0.0035
V6	31	-75	-13	10	33	87	32	-57	-14.5	11	30.5	110	0.9616
V7	29	-51	-21	-2	37	187	32	-86	-8	11.5	24.5	133	0.7072
V8	26	-71	-17	1	24	162	29	-25	5	12	37	143	0.0839
V9	29	-57	-23	11	36	63	32	-45	-13	1	41	135	0.9770
V10	26	-55	-17	4.5	39	179	28	-31	-13.5	7	33	140	0.5974
V11	24	-71	-21.5	10	33	173	29	-78	-9	5	31	145	0.9004
V12	24	-69	-16.5	1.5	46	130	29	-41	-11	8	44	121	0.6358
V13	23	-61	-35	6	28	70	26	-62	-17	4.5	42	125	0.4769

Supplementary Table 10 Change in CK total (G/L) from Baseline (Safety Set)

		Treatment group										
		Clozapine					*Olanzapine*					
		Change in CK total					*Change in CK total*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	33	-705	-28.00	-9.00	4.00	160	38	-163	-51.00	-4.50	23.00	907	0.7997
V3	33	-775	-23.00	-1.00	18.00	147	36	-103	-36.00	6.00	27.00	3528	0.4747
V4	30	-974	-23.00	-1.50	21.00	152	32	-297	-61.00	-6.00	32.50	603	0.9270
V5	28	-1012	-35.50	-8.00	7.50	241	31	-342	-58.00	-1.00	38.00	721	0.6542
V6	28	-923	-32.50	-5.50	15.00	396	31	-170	-36.00	4.00	34.00	281	0.6057
V7	28	-611	-48.00	-2.00	45.00	977	29	-296	-47.00	-6.00	19.00	1207	0.6377
V8	26	-964	-20.00	-0.50	49.00	4027	29	-323	-43.00	-17.00	17.00	1794	0.1856
V9	29	-965	-17.00	-2.00	38.00	334	31	-336	-37.00	4.00	54.00	404	0.9469
V10	25	-1004	-19.00	21.00	44.00	348	28	-213	-42.00	-5.50	24.50	71	0.1030

Supplementary Table 11 Change in CRP (mg/dl) from Baseline (Safety Set)

		Treatment group										
		Clozapine					*Olanzapine*					
		Change in CRP					*Change in CRP*					
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-3.48	0.00	0.02	0.14	3.80	37	-2.94	-0.04	0.00	0.00	1.33	0.0533
V3	32	-2.40	0.00	0.19	0.44	9.55	36	-2.96	-0.05	0.00	0.03	1.24	0.0003
V4	30	-3.24	0.00	0.12	0.30	3.74	32	-2.92	-0.11	0.00	0.07	0.62	0.0019
V5	28	-3.56	0.00	0.04	0.22	5.30	32	-2.92	-0.03	0.02	0.09	1.18	0.3050
V7	28	-2.80	0.00	0.03	0.21	1.41	29	-2.94	0.01	0.10	0.30	2.30	0.5177
V9	29	-3.59	0.00	0.16	0.28	3.99	32	-2.91	-0.02	0.01	0.10	2.20	0.2151

Supplementary Table 12 Change in Troponin (ng/dl) from Baseline (Safety Set)

	Treatment group											
	Clozapine					*Olanzapine*						
	Relative change in Troponin					*Relative change in Troponin*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V2	34	-0.27	0.00	0.00	0.00	0.60	37	-0.40	0.00	0.00	0.00	1.50	0.7277
V3	32	-0.50	0.00	0.00	0.00	0.60	36	-0.25	0.00	0.00	0.00	9.00	0.8856
V4	29	-0.31	0.00	0.00	0.00	4.00	32	-0.33	0.00	0.00	0.00	28.50	0.8474
V5	27	-0.46	0.00	0.00	0.00	5.00	31	-0.33	0.00	0.00	0.00	5.50	0.7011
V7	27	-0.50	-0.14	0.00	0.00	5.00	28	-0.33	0.00	0.00	0.00	29.00	0.4700
V9	29	-0.85	0.00	0.00	0.00	0.67	31	-0.33	0.00	0.00	0.00	2.25	0.5987

Supplementary Table 13 Two-fold Elevated Troponin (Safety Set)

	Treatment group				
	Clozapine		Olanzapine		p-value
	N	n %	N	n %	
Two-fold elevated Troponin *(n, %)*					
Screening	34	0	39	0	
V2	34	0	37	0	
V3	32	0	36	0	
V4	29	1 (3.5 %)	32	1 (3.1 %)	1.000
V5	27	0	31	0	
V7	27	0	28	0	
V9	29	0	31	0	

Supplementary Table 14 Change in Heart Rate from Baseline (Safety Set)

	Treatment group											
	Clozapine					*Olanzapine*						
	Change in Heart Rate					*Change in Heart Rate*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V3	31	-9	10	21	29	58	36	-33	-12	-3.5	7	30	<.0001
V5	26	-13	4	14	29	51	31	-25	-9	-3	4	20	<.0001
V7	27	-15	9	15	26	50	27	-30	-12	-2	6	18	<.0001
V9	28	-29	2.5	11	27	59	32	-32	-14.5	-5	5.5	29	0.0005

Supplementary Table 15 Change in QT Time from Baseline (Safety Set)

		Treatment group											
		Clozapine					*Olanzapine*						
		Change in QT Time					*Change in QT Time*						
visit	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*N*	*Min*	*P25*	*Median*	*P75*	*Max*	*p-value*
V3	31	-86	-42	-22	-6	30	36	-80	-19	1	19	42	0.0003
V5	26	-80	-40	-21	2	28	31	-80	-10	6	26	50	0.0022
V7	27	-88	-45	-20	2	46	27	-70	-6	10	22	60	0.0014
V9	28	-102	-43	-13	-1	52	32	-60	-9	9	25	50	0.0024

Supplementary Table 16 Other clinical assessments (ITT)

		Treatment group							
		Clozapine				Olanzapine			
Change from baseline	N	Min	Median	Max	N	Min	Median	Max	p-value
TALD (V9)	25	-28	-10	10	28	-29	-7	8	0.2767
CGII (V5)	25	-2	2	6	27	-2	3	4	1.0000
CGII (V9)	29	-2	2	4	29	-3	3	5	0.2701
CGIS (V5)	25	-2	0	0	29	-3	-1	0	0.2429
CGIS (V9)	29	-3	-1	0	31	-3	-1	0	0.8891
PSP (V9)	28	0	13	40	31	-10	12	90	0.6206
GAF (V5)	25	-6	6	34	29	-5	9	39	0.3133
GAF (V9)	29	0	15	45	31	-6	11	40	0.3549
CDSS (V5)	25	-8	-2	6	30	-11	-2.5	11	0.7992
CRSS (V9)	26	-12	-2.5	7	31	-14	0	4	0.6410
TMT total (V9)									
Speed	22	-230	-13.5	431	29	-73	-14	61	0.9318
Errors	22	-5	0	12	29	-5	0	4	0.0847
ISST (V9)	27	-12	0	6	31	-5	0	13	0.0842
Q-LES-Q-18 (V9)	26	-20	6.5	45	29	-30	5	36	0.6855
SF-12 (V9)									
Physical	26	-20.4	1.8	22.8	26	-13.0	4.1	22.6	0.4925
Mental	26	-20.0	4.6	36.9	26	-17.9	6.6	32.1	0.3847
DAI10 (V9)	26	-6	0	14	28	-6	2	12	0.1529
SWN-K (V9)	22	-25	1.5	43	28	-73	7.5	49	0.4754

Baseline=BL (V1); week 1 (V2); week 2 (V3); week 3 (V4); week 4 (V5); week 5 (V6); week 6 (V7); week 7 (V8); week 8 (V9)

Supplementary Table 17 Other safety assessments (safety set)

	Treatment group							
	Clozapine				Olanzapine			
Change from baseline	N	Min	Median	Max	N	Min	Median	Max	p-value
GASS (V3)	29	-28.00	0.00	12.00	32	-17.00	-2.50	17.00	0.1783
GASS (V5)	25	-12.00	0.00	13.00	26	-24.00	-3.00	15.00	0.1621
GASS (V9)	26	-25.00	-1.00	18.00	28	-25.00	-3.00	18.00	0.5789
St. Hans Rating Scale (V9)									
Subjective Akathisia Score	28	-5.00	0.00	1.00	30	-5.00	-1.00	4.00	0.3846
Objective Akathisia Score	28	-5.00	0.00	0.00	30	-4.00	0.00	1.00	0.4241
Dystonia Score	28	-1.00	0.00	0.00	30	-2.00	0.00	1.00	1.0000
Parkinsonism Total Score	28	-16.00	-1.00	7.00	30	-14.00	-2.00	8.00	0.5410
Hyperkinesia Total Score	28	-6.00	0.00	6.00	30	-11.00	0.00	0.00	0.0643
CCCS (V3)	29	-7.00	-1.00	7.00	32	-5.00	0.00	4.00	0.8374
CCCS (V5)	25	-7.00	0.00	5.00	27	-6.00	-1.00	5.00	0.0929
CCCS (V9)	27	-8.00	0.00	7.00	28	-7.00	-1.50	5.00	0.3040
BARS (V9)									
Total	28	-8.00	-1.00	1.00	32	-7.00	-1.00	4.00	0.6423
Global	28	-4.00	0.00	1.00	32	-3.00	0.00	1.00	0.2607
Weight (V5)	25	-2.20	1.70	7.00	29	-2.30	2.00	11.00	0.1953
Weight (V9)	28	-6.30	2.00	12.00	30	-3.00	3.40	10.00	0.2620
BMI (V5)	25	-0.80	0.50	2.40	29	-1.00	0.60	3.60	0.2080
BMI (V9)	28	-1.70	0.75	4.00	30	-1.20	1.10	3.40	0.1963
Systolic BP (V2)	33	-19.00	1.00	19.00	35	-29.00	-2.00	12.00	0.3051
Systolic BP (V3)	30	-30.00	3.50	21.00	34	-32.00	-2.00	21.00	0.0400
Systolic BP (V4)	26	-30.00	-1.00	13.00	31	-29.00	-5.00	16.00	0.4804
Systolic BP (V5)	25	-24.00	-4.00	16.00	29	-27.00	-1.00	20.00	0.5433
Systolic BP (V6)	25	-30.00	-1.00	13.00	27	-20.00	-3.00	28.00	0.7623
Systolic BP (V7)	26	-30.00	-2.00	25.00	27	-28.00	-5.00	13.00	0.4439
Systolic BP (V8)	25	-26.00	-1.00	19.00	27	-27.00	-4.00	18.00	0.3992
Systolic BP (V9)	28	-35.00	0.00	30.00	30	-32.00	-3.00	17.00	0.2460
Diastolic BP (V2)	33	-15.00	2.00	20.00	35	-19.00	-2.00	29.00	0.3050
Diastolic BP (V3)	30	-7.00	5.50	26.00	34	-25.00	0.00	21.00	0.0011
Diastolic BP (V4)	26	-19.00	3.00	16.00	31	-24.00	-3.00	17.00	0.0121
Diastolic BP (V5)	25	-16.00	2.00	15.00	29	-23.00	0.00	30.00	0.2172
Diastolic BP (V6)	25	-15.00	0.00	21.00	27	-36.00	0.00	15.00	0.3174
Diastolic BP (V7)	26	-17.00	-0.50	22.00	27	-21.00	1.00	12.00	0.3230
Diastolic BP (V8)	25	-11.00	5.00	31.00	27	-23.00	-1.00	12.00	0.0072
Diastolic BP (V9)	28	-10.00	4.00	23.00	30	-20.00	-1.00	23.00	0.1409

	Treatment group							
	Clozapine				Olanzapine			
Change from baseline	N	Min	Median	Max	N	Min	Median	Max	p-value
Heart rate (V2)	33	-21.00	7.00	29.00	35	-19.00	1.00	38.00	0.0220
Heart rate (V3)	30	-12.00	12.00	54.00	34	-26.00	-1.00	21.00	<.0001
Heart rate (V4)	26	-15.00	11.50	45.00	31	-29.00	-3.00	19.00	<.0001
Heart rate (V5)	25	-13.00	11.00	45.00	29	-28.00	-5.00	35.00	0.0010
Heart rate (V6)	25	-15.00	10.00	37.00	27	-21.00	-6.00	24.00	0.0030
Heart rate (V7)	26	-19.00	6.50	42.00	27	-22.00	0.00	25.00	0.0124
Heart rate (V8)	25	-28.00	7.00	63.00	27	-30.00	1.00	12.00	0.0041
Heart rate (V9)	28	-26.00	9.50	49.00	30	-36.00	-6.00	16.00	0.0023
No. cigarettes per day (V3)	23	-30.00	0.00	10.00	23	-17.00	-1.00	10.00	0.7149
No. cigarettes per day (V5)	23	-25.00	-1.00	8.00	23	-17.00	-2.00	10.00	0.5498
No. cigarettes per day (V6)	23	-25.00	-5.00	9.00	23	-17.00	-2.00	10.00	0.3898
No. cigarettes per day (V9)	23	-25.00	-3.00	20.00	23	-17.00	-2.00	5.00	0.5112

Baseline=BL (V1); week 1 (V2); week 2 (V3); week 3 (V4); week 4 (V5); week 5 (V6); week 6 (V7); week 7 (V8); week 8 (V9)

Supplementary Table 18 IP Blood Levels (ug/L)

	Treatment group											
Visit	Clozapine						Olanzapine					
	N	Min	P25	Median	P75	Max	N	Min	P25	Median	P75	Max
V3	31	0	109	178	308	676	33	2.25	8.20	11.10	17.10	73.40
V5	26	10	194	240	317	697	28	2.05	11.95	17.40	23.90	42.20