Effects of Early Clozapine Treatment on Remission Rates in Acute Schizophrenia (The EARLY Trial): Protocol of a Randomized-Controlled Multicentric Trial

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ABSTRACT

Background Quick symptomatic remission after the onset of psychotic symptoms is critical in schizophrenia treatment, determining the subsequent disease course and recovery. In this context, only every second patient with acute schizophrenia achieves symptomatic remission within three months of initiating antipsychotic treatment. The potential indication extension of clozapine—the most effective antipsychotic—to be introduced at an earlier stage (before treatment-resistance) is supported by several lines of evidence, but respective clinical trials are lacking.

Methods Two hundred-twenty patients with acute non-treatment-resistant schizophrenia will be randomized in this double-blind, 8-week parallel-group multicentric trial to either clozapine or olanzapine. The primary endpoint is the number of patients in symptomatic remission at the end of week 8 according to international consensus criteria ('Andreasen criteria'). Secondary endpoints and other assessments comprise a comprehensive safety assessment (i. e., myocarditis screening), changes in psychopathology, global functioning, cognition, affective symptoms and quality of life, and patients' and relatives' views on treatment.

Discussion This multicentre trial aims to examine whether clozapine is more effective than a highly effective second-generation antipsychotics (SGAs), olanzapine, in acute schizophrenia patients who do not meet the criteria for treatment-naïve or treatment-resistant schizophrenia. Increasing the likelihood to achieve symptomatic remission in acute schizophrenia can improve the overall outcome, reduce disease-associated burden and potentially prevent mid- and long-term disease chronicity.

Introduction

The outcome of relapsing schizophrenia is still unsatisfactory since remission rates in first-episode schizophrenia have been reported to be above 50 % after an antipsychotic treatment of 4 to 6 weeks [1, 2]. Further, at least two out of three patients with schizophrenia develop, despite this high initial efficacy of antipsychotics, an unfavourable disease course [3] with multiple relapses, impaired global functioning, poor quality of life and subsequent secondary treatment resistance. While the reasons for such unfavourable outcomes are multifaceted, including early termination of antipsychotics, the stability of the social network, the access to the mental healthcare system, including early intervention centres and environmental factors, the reduced likelihood of an antipsychotic response in post-first-episode psychosis must be acknowledged as one important factor. Meta-analytic data from 167 double-blind, randomized controlled trials with 28102 participants indicate a good antipsychotic response in patients with an acute exacerbation of non-first-episode schizophrenia only in 23 % of the studied cases [4]. Though still far better than a placebo, with a remarkable number-needed-to treat of eight [4], the efficacy of antipsychotics in relapsing schizophrenia is still unsatisfactory. In this regard, one should consider the superior efficacy of clozapine in treatment-resistant schizophrenia as recommended in national and international treatment guidelines [5, 6]. Moreover, various meta-analyses suggest that clozapine is a generally more efficacious antipsychotic, i. e., its superiority is not restricted to treatment-resistant patients [7–11]. As suggested in 2013, the early application of clozapine before the criteria of treatment-resistance are fulfilled should always be discussed as one possibility to improve outcomes in relapsing schizophrenia [12]. This issue of a potential indication extension of clozapine from being the last-resort, third-line antipsychotic to being applied at an earlier stage (second-line treatment) is supported by several lines of evidence, but respective clinical trials to test this hypothesis are lacking. These lines of evidence [12, 13] are that (1) contrary to treatment with the first antipsychotic, the response rates for consecutive treatments with non-clozapine antipsychotics are low, (2) clozapine is the most effective antipsychotic for treatment-resistant cases and (3) clozapine treatment is associated with earlier and longer remission intervals [12]. Recently published clinical studies [2] and meta-analyses [14, 15] support the idea of an early application of clozapine. Finally, in contrast to guideline recommendations [16–19], clozapine use is delayed by many years in clinical practice, making clear that more convincing evidence is needed to overcome this discrepancy [20].

Based on this theoretical framework and recent evidence, the design of the "Effects of early clozapine treatment on remission rates in acute schizophrenia (EARLY)" was developed. EARLY will test the hypothesis that an early application of clozapine in acute schizophrenia, not fulfilling the criteria for being treatment-naïve nor fulfilling the criteria for treatment-resistance, is superior to treatment with one of the most effective antipsychotics (olanzapine) in achieving symptomatic remission. Thus, (1) EARLY will allow testing of the theoretical framework of "early clozapine" in a randomized-controlled trial design, (2) provide a comprehensive risk-benefit evaluation of early clozapine application and (3) allow treatment guideline developers to evaluate the efficacy of early clozapine application with a high level of evidence.

Methods

Study design

EARLY is a prospective, randomized, actively controlled, double-blind and parallel group multi-centre Phase III clinical trial with a total of 11 German study sites involved. The trial was classified as Phase III according to the recommendations of the ethical board and the federal authorities. The reasons were that this is not a first-in-patient study and was powered for efficacy. The trial protocol has been approved by the local ethics committees and the medical regulatory authorities in Germany (Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)). Prior to the inclusion of the first patient, the

study was registered in the EU Clinical Trials Register (2018-001514-15) and the International Clinical Trials Registry Platform (ICTRP, http://apps.who). The complete trial protocol, as submitted to the authorities with free access, is available in the most recent version at: https://drks.de/search/de/trial/DRKS00016043 and https://trialsearch.who.int/Trial2.aspx?TrialID = DRKS00016043. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [21, 22] checklist is presented in the Supplement.

Study population

Inclusion criteria were as follows: (1) patients aged between 18 and 65 years, with (2) signed informed consent and a (3) DSM-V diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview [23] and (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. Furthermore, (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), 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 paliperidone palmitate as a 3-monthly injection), an inclusion is possible if the 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. Another inclusion criterion is (6) the clinical need for a medication switch because of clinical inefficacy or side effects or the clinical need for a reintroduction of antipsychotic treatment after treatment discontinuation prior to the screening phase (see 5.). Finally, (7) patients must have moderate symptomatology on the Positive and Negative Syndrome Scale (PANSS) [24], 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. Participation in the EARLY trial is possible for (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.

Exclusion criteria were defined as follows: (1) Patients who are not suitable for the study in the opinion of the investigator and (2) patients who are unable to give informed consent as well as (3) coercive treatment at the time of study inclusion. Furthermore, patients with a (4) white blood cell count (WBC) at inclusion not meeting the requirements for clozapine use in Germany were excluded. Patients must have normal leukocyte findings (white blood cell count ≥ 3500/mm^3 (≥ 3.5 × 10^9/l) and Absolute Neutrophil Count ≥ 2000/mm^3 (≥ 2.0 × 10^9/l) at the screening visit. Furthermore, (5) the presence of one or more contraindications against any of the study drugs as mentioned in the Summary of Product Characteristics (SmPC). Another exclusion criterion is the presence of (6) treatment-naïve or treatment-resistant schizophrenia. Treatment-naïve is defined as having no previous antipsychotic treatment or a maximum of 30 days of treatment. Treatment-resistance is defined as two antipsychotic trials (with antipsychotics from two different chemical classes) for a period of ≥ 6 weeks with chlorpromazine (CPZ) equivalent doses ≥ 600 mg/day, both of which took place immediately before the screening phase. Furthermore, (7) the diagnosis of a primary substance dependency other than nicotine is an exclusion criterion, as well as (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 and (10) pregnancy (incl. positive blood pregnancy test)/lactation (female patients).

The aim was to define a study population with a recurrent schizophrenia disease course not fulfilling the criteria for treatment-resistance. To exclude patients with treatment-resistance, an operationalized consensus definition was selected [19]. Treatment-naïve patients were excluded due to the high response and remission rates of these patients to any antipsychotic treatment.

Intervention

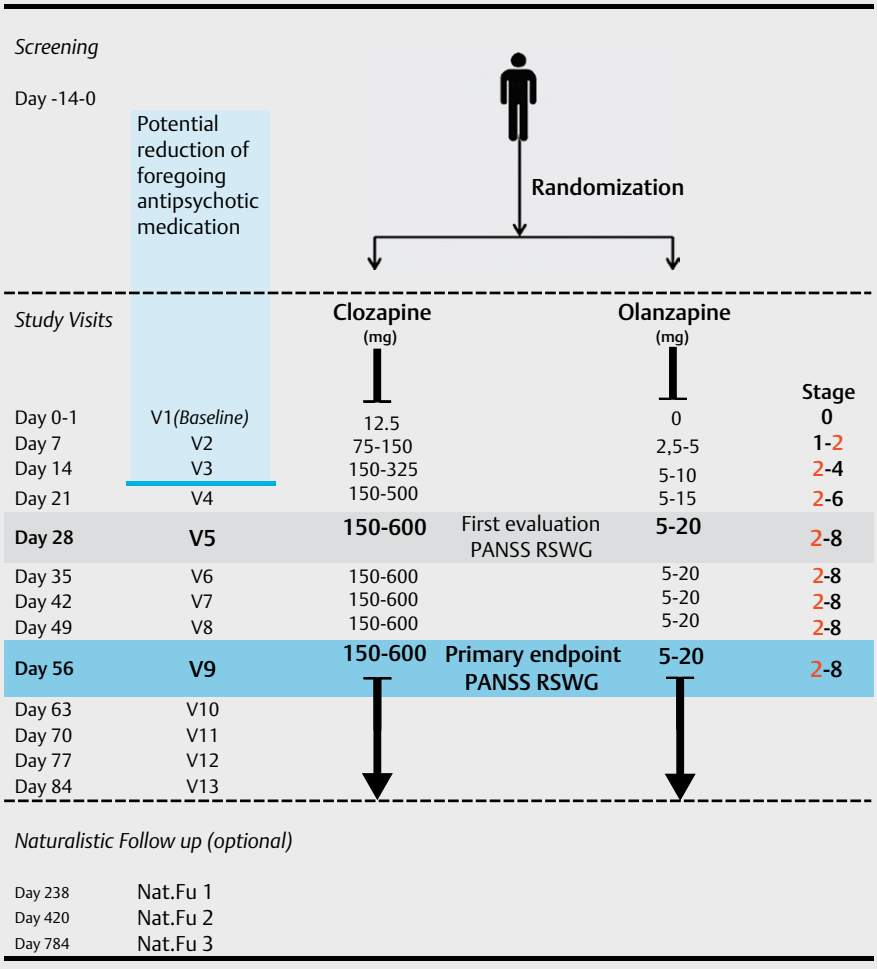
Patients are randomized either to double-blind clozapine or olanzapine and treated for 8 weeks. Clozapine and olanzapine are, to a certain extent, comparable in terms of weight gain/appetite increase, motor side effects, sedation and obstipation – thus, the risk of accidental unblinding due to compound-specific side effects are reduced as much as possible, as shown in a head-to-head trial in individuals with treatment-resistant schizophrenia [25]. Moreover, olanzapine is one of the most-effective non-clozapine antipsychotics [26–28] challenging clozapine in terms of efficacy in our target population of non-treatment-resistant schizophrenia patients.

Randomisation

Central randomization will be performed using predefined randomisation lists, which are stratified by center and created at the Muenchner Studienzentrum (MSZ) using RANCODE professional (version 3.6, IDV, Gauting, Germany) and permuted blocks. The randomization lists are forwarded to the pharmacist at the central pharmacy (University of Heidelberg), who prepares the blinded study medication accordingly. Both patient and treating physician are blinded during the double-blind phase.

Patients have the right to withdraw the informed consent at any time with no reason given and are then declared a drop-out. The investigator, on the other hand, has the right to exclude a patient from the study in the event of concomitant disease, adverse events, therapy failure or any other reason or condition that warrants withdrawal in the interest of the patient. Such patients are not primarily defined as dropouts. All patients leaving the trial prior to visit 9 but accepting the assessment of the primary endpoint at the timepoint of visit 9 (+ 1 week) are no dropouts.

The study flow-chart is presented in ▶ **Fig. 1**. The total study period after randomization is 12 weeks for every patient, including 8 weeks of intervention and 4 weeks of safety follow-up. Pa-



▶ **Fig. 1** Schematic study flow chart.; BL: baseline; FU: Follow-up; PANSS RSWG items: remission criteria according to the Remission in Schizophrenia Working Group; V1-V13: Visit 1 - Visit 13.

tients finishing the double-blind treatment phase are invited to participate in the naturalistic extension study that is not part of the primary study (see ▶ **Table 4**). To be included in the naturalistic follow-up after 12 weeks, patients will have to sign an additional consent form.

Medication

The dose range of clozapine will be 75–600 mg/day and for olanzapine the dose range will be 2.5–20 mg/day and eight dosing stages have been defined for the trial: stage 1 (75 mg clozapine/2.5 mg olanzapine); stage 2 (150 mg clozapine/5 mg olanzapine); stage 3 (225 mg clozapine/7.5 mg olanzapine); stage 4 (300 mg clozapine/10 mg olanzapine); stage 5 (375 mg clozapine/12.5 mg olanzapine); stage 6 (450 mg clozapine/15 mg olanzapine); stage 7 (525 mg clozapine/17.5 mg olanzapine) and stage 8 (600 mg clozapine/20 mg olanzapine). The detailed titration scheme is displayed in ▶ **Fig. 1** and ▶ **Tables 1,2**. Dosage can be adjusted to higher or lower dosages within the listed ranges if a patient fails to improve or if patients develop relevant side-effects. The maximum clozapine of 600 mg/d clozapine corresponds [29] to the approved maximum dose of olanzapine (20 mg) but is below the dosages offered in trials conducted in treatment-resistant patients, which allowed up to 900 mg/day. However, the mean dose actually reached in the double-blind treatment-resistant patients trials were, e. g., 400 mg [25], 304 mg [30] or 291 mg [31]; one meta-analysis analysed trials of treatment-resistant schizophrenia patients and showed that the mean clozapine dose was only 392 mg/d [32]. Furthermore, the patients in our study are not treatment-resistant, so we do not expect them to require such high doses as did the treatment-resistant patients in the earlier studies and the selected maximum dose was chosen to match as good as possible to the maximum dose of 20 mg olanzapine. Our semi-flexible dosing scheme was chosen to allow patients and study doctors to find an optimal individual dose and allowing to develop a double-blind titration scheme with the minimum possible amount of study drug to be manufactured.

The titration schemes of both drugs are the same to maintain the blind (see ▶ **Tables 1,2**). Dosages should be increased to a maximum of one capsule per day of the titration blister (25 mg clozapine/capsule or placebo) from the day after the start of titration dur-

▶ **Table 1** Stages and dose ranges of the trial. The rules for using the lowest dosages (clozapine 75 mg/olanzapine 2.5 mg). V = visit.

Stage 1	75 mg clozapine or 2.5 mg olanzapine, earliest timepoint: V2
Stage 2	150 mg clozapine or 5 mg olanzapine, earliest timepoint: V2
Stage 3	225 mg clozapine or 7.5 mg olanzapine, earliest timepoint: V3
Stage 4	300 mg clozapine or 10 mg olanzapine, earliest timepoint: V3
Stage 5	375 mg clozapine or 12.5 mg olanzapine, earliest timepoint: V4
Stage 6	450 mg clozapine or 15 mg olanzapine, earliest timepoint: V4
Stage 7	525 mg clozapine or 17,5 mg olanzapine, earliest timepoint: V5
Stage 8	600 mg clozapine or 20 mg olanzapine, earliest timepoint: V5

▶ **Table 2** Minimal and maximal dose ranges for the study visits.

V1 (day 0–**1**)	**12.5 mg** clozapine or **0 mg** olanzapine
V2 (day 7)	75–150 mg clozapine or 2.5–5 mg olanzapine
V3 (day 14)	150–325 mg clozapine or 5–10 mg olanzapine
V4 (day 21)	150–500 mg clozapine or 5–15 mg olanzapine
V5 (day 28)	150–600 mg clozapine or 5–20 mg olanzapine
V6 (day 35)	150–600 mg clozapine or 5–20 mg olanzapine
V7 (day 42)	150–600 mg clozapine or 5–20 mg olanzapine
V8 (day 49)	150–600 mg clozapine or 5–20 mg olanzapine
V9 (day 56)	150–600 mg clozapine or 5–20 mg olanzapine

ing the first week. The dose has to be increased by using capsules of the titration blister until stage 1 (75 mg clozapine or 2.5 mg olanzapine/day) has been reached, which should be preferably 3 to 7 days after day 1. Next, dosage should be up-titrated until stage 2 (150 mg clozapine or 5 mg olanzapine/day) has been reached. Stage 2 is the minimal target dosage in this trial and dosage below stage 2 (namely stage 1) is only permitted due to tolerability reasons and this down titration must be documented. Dosage can be adjusted to higher or lower dosages if a patient fails to improve or if patients develop relevant side-effects. Titration can be slowed or stopped below the target dose if subjects cannot tolerate the standard titration schedule because of adverse effects. A daily dosage of < 2.5 mg (stage 1) for > 7 consecutive days and a daily dosage over 20 mg/d for > 3 consecutive days both constitute a protocol violation. The visit corresponding to visit 9 must be scheduled for week 8 where RSWG criteria must be assessed. At visit 9, participants and responsible study doctors will be asked to estimate whether the given participant was in the clozapine or olanzapine treatment arm. Unused patient-specific study medication and used blisters will be returned at visit 9 to assess adherence. Moreover, blinded blood levels, as detailed below, will also be used to assess adherence.

Comedication

The use of antipsychotics in addition to the study medication is not permitted from one day after visit 3 until visit 9 (see ▶ **Fig. 1** and ▶ **Table 3**). During the 2-week titration phase after randomization, the on-demand use of haloperidol (max. 10 mg/day) is permitted as rescue medication in accordance with previous trials [25]. Prestudy antipsychotics will be tapered down during the titration phase and from day 15 onwards, only study antipsychotics are permitted. Treatment with antidepressants is only permitted in cases of clinically relevant depression (Calgary Depression Scale for Schizophrenia sum score > 6 with depressive symptoms for a minimum of 2 weeks) and only if antidepressants are used that do not have relevant interactions with any of the study drugs. The introduction of mood-stabilizers during the trial is not permitted. Pretrial mood-stabilizers can be continued if the used compounds do not have relevant interactions with any of the study drugs. All drugs to treat somatic conditions are permitted if the used substances do not have relevant interactions with any of the study drugs.

Blood levels

Blinded blood levels of clozapine (and desmethylclozapine) and olanzapine (desmethylolanzapine) will be measured 2 and 4 weeks after randomization at visits 3 and 5 at the central laboratory of the Klinikum der Universität München. If the assessment of the blood levels is not possible at these visits, the respective blood draw for blood level analyses should be performed at the next planned visit. All sites will send blood to this central laboratory via the Department of Psychiatry and Psychotherapy at the Klinikum der Universität München. If the reference ranges of the trial drugs have not been reached and patients have not obtained remission criteria (assessed at visits 5 and 7), the dose should be increased to reach blood levels within the recommended range. To avoid unblinding, investigators, patients and raters will only receive blinded qualitative information about the drug levels. Thus, the rater will be informed whether the blood level of the patient is within the therapeutic range or not and the actual blood level of the investigational drug will be graded according to the following ranges:

1) *below (<) the recommended therapeutic range*
2) *lower third within the recommended therapeutic range*
3) *middle third within the recommended therapeutic range*
4) *upper third within the recommended therapeutic range*
5) *above (>) the recommended therapeutic range, but below the warning threshold*
6) *warning threshold*

The quantitative information of the drug levels will be stored blinded at the laboratory and included post hoc in the study database after the end of the study for further statistical analyses. Investigators will only receive the descriptive information detailed above.

Endpoints and safety measures

The *primary endpoint* is the relative frequency of patients in remission after 8 weeks according to the RSWG (Remission in Schizophrenia Working Group) criteria [33], without the time criterion [34, 35]. The RSWG criteria [33] link DSM-IV symptoms of schizophrenia with items of the PANSS [24]. As detailed elsewhere [33, 36, 37], three symptom clusters need to be considered: (1) psychoticism/reality distortion (PANSS items: delusions, unusual thought content and hallucinatory behaviour), (2) disorganisation (PANSS items: conceptual disorganisation and mannerisms/

▶ **Table 3** Frequency and scope of study visits.

Study Visit	**Screening** ##	**Baseline 1** ###	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day	**–14 to 0**	**0–1**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56 Primary Endpoint***	**63**	**70**	**77**	**84 (EOS)**
Intervention of medication		***Administration from day 1 to day 56***												
Informed consent	X ****													
Inclusion/exclusion criteria	X													
Drug screening	X													
AUDIT interview and MINI	X													
Fagerström test (Smoker)		X												
Demographic data/medical/ Psychiatric history	X													
Pre-study medication	X	X	X	X										
Physical examination	X	X	X	X	X	X	X	X	X	X				
Study laboratory	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X													
Number of cigarettes		X		X		X	X			X				
Interaction check******		X	X	X	X	X	X	X	X	X				
PANSS ***,#	X	X				X				X				
PANSS RSWG items	X	X				X		X		X				
CGI and GAF		X				X				X				
PSP, ISST, Trail-Making-Test (TMT)		X								X				
CDSS		X				X				X				
Q-LES-Q-18, SF-12, DAI10, SWN-K, TALD		X								X				
Attitude towards clinical trials		X												
BARS		X								X				
GASS		X		X		X				X				
St. Hans Rating Scale (SHRS)		X								X				
CCCS		X		X		X				X				
Assessment blood pressure and heart rate		X	X	X	X	X	X	X	X	X				
Assessment of weight and BMI		X				X				X				
EEG		X								X				
ECG	X	X		X		X		X		X				
Study medication (re-) dispensing		X	X	X	X	X	X	X	X	*				
Study medication return										X				

▶ **Table 3** Frequency and scope of study visits.

Study Visit	**Screening ##**	**Baseline 1 ###**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Day	**−14 to 0**	**0–1**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56 Primary Endpoint***	**63**	**70**	**77**	**84 (EOS)**
Blood draw drug levels **				X		X								
Assessment of blinding integrity										X				
Discontinuation check		X	X	X	X	X	X	X	X					
SAE/AE		X									X*****			
Concomitant medication		X									X*****			

AUDIT: Alcohol Use Disorders Identification Test; MINI: MINI-Interview for ICD-10 and DSM-V diagnosis; PANSS: Positive and Negative Syndrome Scale; PANSS RSWG items: Remission criteria according to the Remission in Schizophrenia Working Group; CGI: Clinical Global Impression scale; GAF: Global Assessment Scale of Functioning; PSP: Personal and Social Performance Scale; ISST: InterSePT scale for suicidal thinking; TMT: Trail-Making-Test, CDSS: Calgary Depression Rating Scale for Schizophrenia; Q-LES-Q-18: Abbreviated quality of life enjoyment and satisfaction questionnaire; SF-12: Short Form Health Survey; DAI-10: The Drug Attitude Inventory; SWN-K: The subjective well-being under neuroleptic scale; TALD: Thought and Language Disorder Scale; BARS: Barnes Akathisia Rating Scale; GASS-C: Glasgow Antipsychotic Side-effects Scale for Clozapine; SHRS: St. Hans Rating Scale; CCCS: Cleveland Clinic Constipation Score; BMI: Body-Mass Index; EEG: electroencephalogram; ECG: electrocardiogram; (S)AE: (Serious) Adverse Event.

* one additional blister of study medication can be distributed to the patient if the patient is discharged from inpatient treatment (lasting for around 4 days)

**Documentation of amount and type of capsules related to the time point of blood draw for drug level assessment; If a blood draw is not possible on the planned visits, the drug levels can be assessed at the next planned visit.

*** During the study visits of the double-blind treatment phase, psychopathological worsening of the patient is documented if the members of the study team performing the current study visit AND/OR the current treating physicians at the time of the study visit suspect a relevant worsening of psychotic symptoms. If psychopathological worsening is suspected in this regard, additional PANSS ratings should be performed in those visits where a PANSS rating is not planned. Psychopathological worsening will then be assessed and defined as an increase of at least 20 % in the PANSS total score. The measure of the increase in PANSS total score is calculated according to the following formula: Δ-PANSS total % = (PANSS total score at current Visit − PANSS total score at Visit Baseline (visit 1))* 100/(PANSS total V Baseline (visit 1) − 30) [%]. Thereby the deterioration in relation to baseline, i. e., visit 1, will be assessed as a measure for worsening throughout the study.

**** Also, in case of relevant psychopathological worsening as defined by the above-mentioned criteria (i. e., an increase in PANSS total score of at least 20 %) or an emerging SAE), a clinician that is not associated with the study (board-certified psychiatrist/Facharzt für Psychiatrie und Psychotherapie) has to reconfirm and document that the patient continues to be capable of giving informed consent. If not, the patient has to be excluded from the study.

***** Concomitant medication will be reported in case of a new laboratory-related AE after visit 9/Early Termination or any SAE between Visit 10–13; after completing visit 9, only laboratory-related AEs and SAEs will be documented.

******Interaction check at baseline can be performed with textbooks, tables or commercial software. Interaction checks from visit 2 - visit 9 have not to be performed with a specific instrument.

NOTE: PANSS rating scores obtained at the Screening Visit (visit 0, V0) can be used for the Baseline Visit (V1, visit 1) within a maximum range of 7 days.

NOTE: If during the course of treatment of inpatients OR outpatients, an ECG and/or an EEG and/or laboratory tests have been performed prior to inclusion into the study (i. e., prior to giving informed consent on the informed consent (IC) form), these can also be used for the study visit V0 (Screening Visit) within the following day ranges: An ECG performed within 7 days before the Screening Visit, can be used for the Screening Visit. EEG recordings are valid for the Screening Visit if they are performed within 5 days prior to the day on which the Screening Visit is performed. Similarly, laboratory tests are valid for the Screening Visit if they are performed within 3 days prior to the day on which the Screening Visit is performed.

NOTE: If an ECG and/or an EEG and/or laboratory tests have been performed prior to inclusion into the study (i. e., prior to giving informed consent on the IC form), these can also be used for visit 1 (Baseline Visit) within the following day ranges: An ECG performed within 7 days before the Baseline Visit, can be used both for the Screening and the Baseline Visit. EEG recordings are valid for the Baseline Visit if they are performed within 5 days prior to the day on which the Baseline Visit is performed. Similarly, laboratory tests are valid for the Baseline Visit if they are performed within 3 days prior to the day on which the Baseline Visit is performed. Finally, the PANSS rating scores obtained at the Screening Visit can be used for the Baseline Visit within a maximum range of 7 days.

▶ **Table 4** Naturalistic follow-up visits N1–N3.

Study Visit	N1	N2	N3
Day	**+26 weeks (D 238+/– 4 weeks) after V9**	**+52 weeks (D 420+/– 4 weeks) after V9**	**+104 weeks (D 784+/– 4 weeks) after V9**
Naturalistic follow-up			
Medical and psychiatric history	**X**	**X**	**X**
Year of birth, Sex	**X**		
Living circumstance, working status	**X**	**X**	**X**
Actual treatment	**X**	**X**	**X**
PANSS	**X**	**X**	**X**
PANSS RSWG items	**X**	**X**	**X**
CGI	**X**	**X**	**X**
GAF	**X**	**X**	**X**
PSP	**X**	**X**	**X**
Q-LES-Q-18	**X**	**X**	**X**
SF-12	**X**	**X**	**X**

PANSS: Positive and Negative Syndrome Scale; PANSS RSWG items: Remission criteria according to the Remission in Schizophrenia Working Group; CGI: Clinical Global Impression scale; GAF: Global Assessment Scale of Functioning; Q-LES-Q-18: Abbreviated quality of life enjoyment and satisfaction questionnaire; SF-12: Short Form Health Survey.

posturing), and (3) negative symptoms (PANSS items: blunted affect, social withdrawal, lack of spontaneity). According to the RSWG criteria, the symptomatic criterion states that to achieve symptomatic remission, all items must be rated as absent or present only to a mild degree (PANSS value ≤ 3).

Secondary endpoints are the relative frequency of patients in remission after 4 weeks (early remission) according to the RSWG criteria [33], the change in PANSS total and in the three PANSS subscales (positive, negative, general) from baseline to week 4 and week 8, the frequency of patients in remission according to the RSWG criteria without the negative symptom Items (N1, N4 and N6) after 4, 6 and 8 weeks, and the frequency of patients with a clinical response according to PANSS (≥ 20 % reduction from baseline, corrected PANSS formula) [35] after 4 and 8 weeks. *Safety secondary endpoints* include the change in white/complete blood count (WBC/CBC), creatinine kinase (CK), blood levels from screening to every visit during the study period (until visit 13), the relative change in Troponin, frequency of 2-fold elevated Troponin, and absolute change in C-reactive protein (CRP) values from screening to every visit during the first 4 weeks of the intervention period and at week 6 and week 8 as well as changes in standard parameters of Electrocardiography (ECG) (QT interval, heart rate value from screening/baseline to week 2, week 4, week 6 and week eight).

Several other assessments have been a priori-defined as detailed in ▶ **Table 3**. These other assessments include among others the relationship between drug blood levels/concentration (see below) and clinical and side-effect endpoints, changes in the Thought and Language Disorder questionnaire (TALD) [38], the Clinical Global Impression scale (CGI) [39], the Personal and Social Performance scale (PSP) [40], the Global Assessment of Functioning scale (GAF) [41], the Calgary Depression Scale for Schizophrenia (CDSS) [42], the Trail-Making Test [43], the InterSePT scale (ISST) [44], the abbreviated quality of life enjoyment and satisfaction questionnaire (Q-LES-Q-18) [45], the Short Form (12) Health Survey Change (SF-12) [46], the Drug Attitude Inventory (DAI10) [47], the Subjective Wellbeing under Neuroleptics short form (SWN-K) [48] scale and the attitude of patients towards participation in clinical research and towards the treatment with olanzapine and clozapine at baseline (self-developed questionnaire, in collaboration with a relatives-driven pan-organisation that represents the interests of relatives and persons affected by mental illness).

Other safety assessments include measurement of vital signs (change in heart rate, blood pressure), change in metabolic parameters (weight and BMI), change in extrapyramidal symptoms according to the Glasgow Antipsychotic Side-effect Scale for Clozapine (GASS for Clozapine) [49] and the St. Hans Rating Scale (SHRS) [50], change in treatment-associated constipation according to the Cleveland Clinic Constipation Score (CCCS) [51], change in akathisia according to the Barnes Akathisia Rating Scale (BARS) [52], changes in the study laboratory (fasting glucose, cholesterol, HDL), changes in the number of cigarettes per day and changes in standard parameters of Electroencephalography (EEG) (see ▶ **Table 3**).

Adverse events (AE), severe adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) are documented following established definitions and legal requirements. The intensity of AEs is defined according to the common terminology criteria for adverse events (CTCAE Version 4.0, https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010–06–14_QuickReference_5×7.pdf). In the event of a medical emergency, there are unblinding envelopes for each patient at the respective study center.

During the safety follow-up period (starts after completed visit 9), only laboratory-related AEs and SAEs will be documented.

A patient-relatives organisation (Bavarian Association of the Relatives of Mentally-ill Patients (LApK)) is involved in the study. The organization participates in the application process, assists in investigating the patients' view on treatment and serves as a consultant for study patients. The aspect of the view of patients on treatment is especially important because some studies have found that psychiatrists and patients have different valuations of clozapine side effects [53], and one Cochrane review states that former trials have neglected patients' attitude towards clozapine [54].

Treatment after the end of the double-blind treatment phase

Unblinding patients at the end of the double-blind treatment phase (until visit 9) is sensitive, as it is not acceptable that the advantages of a double-blind study are diminished by the possibility of changing previously collected data after the treatment is unblinded. Therefore, a standard operating procedure (SOP) was implemented on the means to continue treatment after the end of the double-blind treatment phase. After visit 9 (day 56), the physicians being responsible for the further treatment receive an envelope with the information in which arm the patient has been allocated (unblinding according to protocol). People involved in the trial will

not receive this information. For patients who drop out prior to visit 9, unblinding according to the protocol will also only be possible following the aforementioned principles.

For patients who meet the remission criteria at week 8, it is recommended to stay on the same drug. For patients who do not meet remission criteria at week 8 and being treated with clozapine, it is recommended to carry on treatment and perhaps increase the dose as clinical knowledge is available that the effect of clozapine may occur with a delay. For patients being treated with olanzapine not meeting remission criteria, it is recommended to increase the dose and, if not successful, switch to clozapine.

However, the decision of any further treatment after visit 9 will be made between the treating physicians and the patients following national guideline recommendations. The study team will not be involved in this decision. Clozapine should not be stopped abruptly but tapered down according to clinical standard procedures. Therefore, our SOP shall assure that patients at the end of the double-blind treatment phase will have enough study medication until the next meeting with their treating physician while aiming at coordinating the meeting with the treating physician on the same day of visit 9.

Sample size justification and planned data analysis strategy

The sample size calculation was performed on the basis of previous studies, meta-analyses and systematic reviews [37, 55–57], which indicate remission rates of approximately 30 % after 4 weeks [34] for antipsychotics in acute schizophrenia and mean remission rates of ~ 50 % after 8 to 12 weeks. Because olanzapine is one of the most effective antipsychotics [26, 58, 59], we proposed a remission rate of 55 % in the non-clozapine group after 8 weeks. Assuming that 55 % (= p2) of acute schizophrenia patients will remit after treatment with olanzapine and assuming a superiority of clozapine in the range of 10 % to 30 % in achieving remission [60] in severely affected patients, we expect that clozapine will be associated with a ≥ 20 % (= p1 – p2) increased likelihood of achieving remission compared to non-clozapine treatment. A two-group Chi^2 test ($\alpha = 0.05$, two-sided, power [1-β]: 80 %) will detect a difference between groups after adjusting p1 (clozapine) to 0.74 and p2 (olanzapine) to 0.56 (odds ratio of 2.236) when the sample size in each group is 110 (computed by nQuery Advisor 7.0). Thus, the total required sample size is 220. The adjustment of relative frequencies is due to the conservative assessment of the primary outcome as outlined below, assuming less than 2 % losses to follow-up with no primary outcome data. As we aim to evaluate the primary outcome in every participant, irrespective of whether he or she discontinues treatment, the estimated rate of 2 % losses to follow-up/drop-outs defines a realistic scenario.

A statistical analysis plan will be developed before any analyses will be performed. The statistical analyses will be performed after the database hard lock (end of study), but before the end of the naturalistic follow-up. The latter is a secondary analysis that will be performed at the end of the naturalistic follow-up period. Descriptive statistics will be provided for all data broken down by treatment group, visit and by country. Mean, median, standard deviation, range, interquartile range and number of observations will describe continuous variables. Absolute and relative frequencies will describe categorical variables. All statistical tests will be carried out in two-tailed, with the alpha (level of significance) being 5 %. The randomization procedure will be evaluated by a comparison of the two treatment groups for all relevant variables recorded at baseline. The primary efficacy endpoint in the intention-to-treat (ITT) population will be compared between groups by a confirmatory Mantel-Haenszel test, with centres as strata on a two-sided significance level of 5 %. The analysis will be performed on the (ITT) population, which will include all patients as randomized. To ensure a conservative assessment of the primary outcome, losses to follow-up in the experimental group will be rated as failures, while those in the control group will be rated as successes. This approach is designed to avoid a beneficial bias for the experimental group, which might be induced by non-compliance and losses to follow-up. An additional subgroup analysis will be performed by logistic regression using the primary efficacy endpoint as the outcome and the factor variables group, centre and the categorized number of previous lifetime treatments (cNLT categories: 0, 1, > 1) as covariates. An interaction effect between the group and the cNLT subgroups will be included in the model. Parameter estimates of the model will be used to obtain point and interval estimates (95 % confidence intervals) of the treatment effect, represented by Odds Ratios, within cNLT subgroups. The hypothesis test on the model's interaction effect equals the test for differences in the treatment effects between subgroups. This subgroup analysis is exploratory and none of the hypothesis tests of effects within and between subgroups is powered by the study's sample size calculation. The major objective is effect estimation instead. Depending on the data distribution, group comparisons of continuous and categorical secondary endpoints will be performed by linear or binary logistic regression analysis that includes a factor variable for centres. Baseline values will be included as another covariate if existing. In the case of non-normally distributed residuals of the linear model, a van Elteren test (= stratified Wilcoxon test) with centres as strata will be applied in an additional analysis. Corresponding descriptive statistics and confidence intervals will also be given. Absolute and relative frequencies of categorical safety outcomes will be assessed along the course of the trial (safety population). Differences between groups will also be tested for statistical significance with Fisher's exact test. Likewise, continuously distributed safety outcomes (safety population) will be presented by descriptive statistics and compared with t-tests or Mann-Whitney U tests, as appropriate. All tests of secondary endpoints will be computed in the ITT and per protocol (PP) populations in an explorative manner on two-sided significance levels of 5 %. Exploratory analyses will be performed as appropriate for other assessments.

The ITT population includes all patients as randomized. The PP population will include all participants without major protocol violations. The safety population will include all participants who received at least one study drug and will be analysed as treated. The allocation of patients to the respective study populations will finally be determined in a blinded data review meeting (BDRM). All analyses will be performed in accordance with the ICH Guidelines E9.

Organizational framework

Organizational project management, safety management, monitoring, data management and randomization are performed by MSZ, an academic clinical research organization of the Technical University of Munich, School of Medicine. A detailed description of this framework is available elsewhere [61]. For safety monitoring, an independent safety monitoring board (SMB) with an SMB Charta has been established. The documentation of the study data in adherence to the Good Clinical Practice (GCP) - guidelines and the clinical trial protocol lies within the responsibility of the investigator and will be performed in a validated clinical trial database. Original data (source documents) remain in hospital medical records. Original written informed consent obtained by qualified study doctors and signed by the patient is kept by the investigator, and a signed copy will be given to the patient. All study procedures are in accordance with GCP guidelines of the international conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH) and the principles of the Declaration of Helsinki. All sites agreed to adhere to the instructions and procedures described in the study protocol and thereby adhere to the principles of ICH-GCP.

Discussion

An early clozapine application, as proposed in the EARLY trial in disease stages after the first episode and before treatment-resistance (second-line treatment), has the potential to increase remission rates and to prevent poor disease outcomes and chronicity in schizophrenia. Poor remission rates and frequent relapses in schizophrenia contribute to the highest direct costs of all brain disorders in Europe, totaling 29 billion Euros per year [62]. Furthermore, early disease chronicity entails physical and mental comorbidity, enduring social and vocational exclusion and excess mortality, which alone in Europe amount to annual indirect costs of 65 billion Euros [62].

Multiple sources of evidence show that schizophrenia patients have a high likelihood of response during their first episode [1] but that response rates drop after the first relapse. In a small naturalistic study, 38 % of first-episode patients were non-responsive to first-line treatment with risperidone and among those non-responders, only 44 % achieved full remission of positive symptoms after treatment with olanzapine (second-line) [63]. As many patients do not remit after the first relapse and as remission is related to recovery [64], good functional outcomes and improved quality of life [56], new evidence-based strategies are urgently needed to increase remission rates. An increase in remission will not only improve the aforementioned outcome domains but is likely to reduce the risks of hospitalization and treatment discontinuation. In this context, the early application of clozapine, the most effective antipsychotic, has been discussed now for years as one possibility to improve outcomes in relapsing schizophrenia [12]. This issue of a potential indication extension of clozapine from being the 'last-resort antipsychotic' to being applied at an earlier stage is supported by several lines of evidence [12], but respective clinical trials to test these hypotheses are lacking. To date, sufficiently powered clinical trials investigating the proposed superior efficacy of an early clozapine application compared to standard treatment are lacking. A retrospective cohort study confirmed the hypothesized superior effectiveness of clozapine compared to standard antipsychotics with regard to time to hospitalization and risk for treatment discontinuation [65], and clozapine is still the gold standard in treatment-refractory cases [16–18]. Moreover, one nationwide cohort study investigated the real-world effectiveness of 29823 patients with schizophrenia and showed the association between clozapine treatment and the lowest rates of treatment failure compared to all other oral antipsychotics [66]. In contrast to guideline recommendations [16–18], in clinical practice, clozapine use is delayed by many years, making clear that more convincing evidence is needed to overcome this discrepancy [20]. We hypothesize that the early introduction of clozapine in patients with acute schizophrenia will result in higher remission frequencies and thus reduce the risk of developing unfavorable disease outcomes. In summary, there is broad evidence that clozapine is an effective antipsychotic that can be safely used in non-treatment-refractory patients and that has superior effectiveness in real-world settings. Clinical trials investigating the role of clozapine in acute relapsing schizophrenia are lacking (second-line treatment). Such an approach also must specifically address the potentially high levels of side effects and AEs to allow for a comprehensive risk-benefit evaluation. An increase in the likelihood of remission has the potential to prevent treatment-resistance and long-standing disability in schizophrenia patients with a relapsing disease course and thus reduce the overall socioeconomic burden. Because neither study drug is under patent protection, no commercial interest for any pharmaceutical company exists. Therefore, this trial has the potential to change guideline recommendations in an area where no new development from the perspective of the pharmaceutical industry can be expected.

Moreover, this trial will also allow investigating whether low dosages of those highly effective antipsychotics are sufficient to reach symptomatic remission following the discussions of minimal effective dose treatment for an optimal risk-benefit evaluation. The latter will be possible because the EARLY trial includes the so far most extensive side-effect evaluation of clozapine and olanzapine in a controlled design going far beyond the safety assessment in clinical practice.

Impact of SarsCov2-Pandemic (Covid-19)

Specific measures were implemented to increase patient and data safety while conducting the trial during the pandemic. A specific risk-based approach dealing with the challenges of the pandemic based on the recommendations laid down in the EMA guidance on the management of clinical trials during the covid-19 (coronavirus) pandemic [67] the recommendations of the Federal Institute for Drugs and Medical Devices (BfArM) [68] and the recommendations of the Work Group of Medical Ethics Commissions in Germany for clinical research during the pandemic [69]. Furthermore, the planned period for patient recruitment had to be substantially prolonged due to restrictions and the impact of the SarsCov2-Pandemic.

Conclusion

In medication-naïve and first-episode patients (first-line treatment), a subtle [14] but not an outstanding superiority of clozapine could be established [12]. These findings can be explained by

the high response and remission rates of first-episode patients [70] and as a result of risk-benefit evaluation, clozapine should not be used for this indication. In treatment-resistant schizophrenia patients [60] (third-line treatment), clozapine is more effective than other antipsychotics [71], but due to the progressed stage of the illness, the application may be too late to increase remission rates significantly. Thus, an early clozapine application, as proposed in the EARLY trial in disease stages after the first episode and before treatment-resistance (second-line treatment), has the potential to increase remission rates and prevent poor disease outcomes and chronicity. Upon completion, it will be the largest randomized, double-blind parallel-group multicentric trial to date to compare the efficacy of clozapine and olanzapine.

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Conflict of Interest

E. Wagner has been invited to advisory boards from Recordati. W. Strube has received a speaker's honorarium from Mag&More GmbH and neurocare and was a member of the advisory board of Recordati. A. Hasan has received speakership fees from Lundbeck, Otsuka, Janssen, Rovi, AbbVie and Recordati. He was member of advisory boards of Boehringer Ingelheim, Lundbeck, Otsuka, Janssen, Rovi, and Recordati. M. Lambert has received honoraria for consultancy and speakers' fees from AstraZeneca, Bristol-Myers Squibb, Lilly Deutschland GmbH, Janssen Cilag GmbH, Lundbeck GmbH, Otsuka Pharma GmbH, Roche Deutschland Holding GmbH, Sanovi Aventis, Trommsdorff GmbH & Co. KG, Takeda Pharma Vertrieb GmbH, and is founder of MiNDNET e-Health-Solutions GmbH. P. Falkai is on the advisory boards and receives speaker fees from Janssen, Lundbeck, Otsuka, Servier and Richter B. Langguth has received honoraria for consultancy and speakers' fees from ANM, AstraZeneca, Autifony Therapeutics, Decibel Therapeutics, Desyncra, Gerson Lehmanns Group, Lundbeck, Merz, MagVenture, Medical Tribune, Neurolite, Neuromod, Novartis, Pfizer, Rovi, Schwabe, Sea Pharma, Servier, Sonova and Sound Therapeutics; All other co-authors report no conflict of interest.

Clinical trial

Trial registration: Prior to the inclusion of the first patient, the study was registered on the International Clinical Trials Registry Platform (https://trialsearch.who.int/Trial2.aspx?TrialID = DRKS00016043) and on the European EudraCT platform with the number 2018-001514-15.

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