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SHORT COMMUNICATION

Evaluation of the Efficacy of BI 425809 Pharmacotherapy in Patients with Schizophrenia Receiving Computerized Cognitive Training: Methodology for a Double-blind, Randomized, Parallel-group Trial

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Abstract

Background and Objective Cognitive impairments associated with schizophrenia (CIAS) predict poor functional outcomes, but there are currently no approved pharmacological treatments for patients with CIAS. Additional cognitive stimulation may be required for pro-cognitive medications to improve efficacy, and computerized cognitive training (CCT) can be used to increase cognitive activity. A trial evaluating the effects of the novel glycine transporter inhibitor BI 425809 compared with placebo, on a background of regularly self-administered CCT in clinically stable patients with schizophrenia has commenced and its methodology is described here.

Methods This Phase II, multinational, randomized, double-blind, placebo-controlled, parallel-group trial will randomize 200 clinically stable outpatients, aged 18–50 years with established schizophrenia and no other major psychiatric disorder, 1:1 to BI 425809 or placebo once daily for 12 weeks. Following screening, which included a 2-week CCT run-in period, patients sufficiently compliant with CCT (target: ≥ 2 h of CCT per week during CCT run-in) will be randomized. During the 12-week treatment period, all patients should complete a total of approximately 30 h of CCT. The primary endpoint is change from baseline in neurocognitive function as measured by the neurocognitive composite score of the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB), after 12 weeks of treatment. Secondary endpoints include change from baseline in overall MCCB score, Schizophrenia Cognition Rating Scale, Positive and Negative Syndrome Scale, and safety (adverse events [AEs]) and serious AEs. Primary and secondary endpoints will be analyzed using the Restricted Maximum Likelihood-based mixed model for repeated measures. Novel endpoints include the Balloon Effort Task to evaluate patients' motivation and the Virtual Reality Functional Capacity Assessment Tool to assess skills for daily functioning.

Discussion This is one of the largest and longest trials to date to combine pharmacological therapy with CCT in patients with schizophrenia and will determine the benefit of combining BI 425809 pharmacotherapy with cognitive stimulation through self-administered CCT. This trial will further evaluate whether improvements in neurocognition translate into improved everyday functioning, whether self-administered CCT can be effectively implemented in a large multinational trial, and the role of motivation in neurocognitive and functional improvements.

Trial Registration Registered on Clinicaltrials.gov on March 1, 2019 (NCT03859973).

1 Introduction

Cognitive impairments associated with schizophrenia (CIAS) consistently predict poor functional outcomes in patients with schizophrenia [1–4]. However, there are currently no approved pharmacological therapies for these cognitive impairments, and a systematic review of available medications targeting neurotransmission found few beneficial effects on cognitive outcomes in patients with schizophrenia [5]. In the absence of effective pharmacological therapies, a variety of learning-based behavioral

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Key Points

Computerized Cognitive Training (CCT) programs can improve general functioning in patients with schizophrenia when combined with rehabilitation approaches.

This trial evaluates the benefits of an augmentation approach combining BI 425809 pharmacotherapy with CCT in patients with schizophrenia.

interventions have been explored. Computerized Cognitive Training (CCT) programs aim to improve general cognitive performance through computerized skills training, which can improve general functioning in patients with schizophrenia when combined with rehabilitation approaches [6, 7]. For example, rehabilitation approaches such as supported employment or social skills training paired with CCT can lead to substantial incremental improvements in real-world outcomes [8, 9]. Success-based reinforcement learning through repetitive practice has been shown to promote activity-dependent neuroplasticity in humans [10], which is the basis of cognition, particularly of learning and memory [11].

Meta-analyses of studies evaluating CCT approaches in patients with schizophrenia suggest that these approaches can result in durable improvements in global cognition, with small to medium effect sizes [12–14]. However, cognitive impairments in schizophrenia are often severe, and augmentation of existing CCT approaches may be required to consistently improve functional outcomes. Therefore, an innovative approach has been explored that involves combining CCT with pro-cognitive pharmacological treatments in patients with schizophrenia [15–19] and in schizotypal personality disorder, a schizophrenia spectrum disorder [20].

At many synapses in the central nervous system, glutamatergic signaling via *N*-methyl-D-aspartate (NMDA) receptors is required for the induction of long-term synaptic neuroplasticity [21, 22]. Modulators of NMDA receptor signaling are therefore promising candidates for pro-cognitive therapy. However, previous trials of modulators of glutamatergic signaling, such as glutamate receptor co-agonists (e.g. D-serine, glycine) and glycine transporter inhibitors (e.g. bitopertin, sarcosine), have produced contradictory results [23–26]. One potential explanation for this is that neuroplasticity is activity dependent (i.e. requires external demands) and that the environment and surroundings of patients with schizophrenia may provide only a low level of cognitive stimulation [27]. It therefore remains unclear whether medications alone, that exert their effect via the enhancement of neuroplasticity, can improve neurocognitive and functional outcomes in these patients, or whether increase in demand-dependent cognitive stimulation is required for these drugs to improve outcomes [19]. CCT may be an effective cognitive enrichment strategy to augment external demands on cognitive activity, and as such may enhance the activity of pro-cognitive agents targeting neuroplasticity.

BI 425809 is a glycine transporter 1 (GlyT1) inhibitor that increases the concentration of glycine in the synaptic cleft [28]. Glycine is an obligatory co-agonist for NMDA receptor activation; inhibitors of synaptic glycine uptake are therefore thought to enhance NMDA receptor signaling [29] and may promote downstream plasticity processes [30]. BI 425809 is generally well tolerated in healthy volunteers, and the most commonly reported adverse events (AEs) in Phase I studies included headache, back pain, nausea, vomiting, and neck pain [31, 32]. A Phase II clinical proof-of-concept and dose-finding study investigating the potential benefits of BI 425809 as add-on therapy to standard of care for CIAS in patients with schizophrenia is currently underway (NCT02832037).

This paper describes the methodology of a trial that evaluates the benefits of an augmentation approach combining BI 425809 pharmacotherapy with enhanced cognitive stimulation through self-administered CCT in patients with schizophrenia. The trial (NCT03859973) will assess the effect of BI 425809 on neurocognition and how its improvement translates to changes in everyday functioning assessed using both rater-based questionnaires and the innovative performance-based virtual reality tests. As previous studies have shown that motivation can influence outcomes in trials of cognitive performance [33–35], this trial will also evaluate patient motivation and the role of such motivation in cognitive functioning.

2 Methods

2.1 Study Design

NCT03859973 is a Phase II, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group trial that was initiated in April 2019, with completion planned for late 2020. The trial aims to randomize 200 patients with schizophrenia across approximately 40 centers in 6 countries (USA, UK, Canada, Australia, France, New Zealand; a full list of study sites is available at clinicaltrials.gov). During the screening period, patients will undergo CCT run-in for 2 weeks. Patients sufficiently adherent with CCT during run-in will be eligible and randomized 1:1 to BI 425809 10 mg or placebo for 12 weeks. The dose was selected based on a Phase I study showing a mean increase in cerebrospinal fluid glycine of approximately 50% after multiple doses of BI 425809

10 mg, demonstrating functional target engagement at this dose [28]. Randomization is stratified by age (≤ 40 years vs > 40 years) using interactive response technology. All randomized patients will receive access to an adjunctive self-administered CCT for the full duration of the 12-week treatment period. A CCT device and any related equipment (e.g. headphones, accessories) will be provided to the patient, if needed (i.e. if a patient does not have or is not willing to use their own device). For each patient, the trial consists of 7 visits. The follow-up visit will occur 4 weeks after the last intake of trial medication, or after early discontinuation of the trial medication.

2.2 Patients

Patients planned for inclusion in the trial will be aged 18–50 (inclusive) years at the time of consent and have established schizophrenia, according to the criteria defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). All must be clinically stable outpatients with no symptom exacerbation or hospitalization for worsening of schizophrenia within 3 months prior to randomization, and with no more than moderate positive symptoms as assessed using the Positive and Negative Syndrome Scale (PANSS). Patients must currently be on stable antipsychotic medication (up to 2 antipsychotics are allowed except for clozapine) for at least 3 months prior to randomization, with no change in dose in the 30-day period prior to randomization. Patients receiving long-acting injectable antipsychotics could be included as long as their medication and dose was unchanged for at least 3 months prior to randomization. Women of childbearing potential must be prepared to use highly effective methods of birth control throughout the trial and for at least 35 days after. All patients must demonstrate their ability to properly use the CCT device and program, be compliant with CCT during the run-in period, and each must have a study partner who should know the patient sufficiently well to provide reliable input into the Schizophrenia Cognition Rating Scale (SCoRS) and PANSS evaluation.

Main exclusion criteria are as follows: a categorical diagnosis of another current major psychiatric disorder; history of completion of a formal cognitive remediation program for at least 10 sessions; patients who participated in a trial with repeated testing on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) within 6 months prior to randomization; significant history of drug abuse disorder within 6 months prior to informed consent or positive urine drug screen at Visit 1; and women who are pregnant, nursing, or who plan to become pregnant while in the trial.

2.3 Endpoints

Study endpoints are listed in Table 1. The primary endpoint is change from baseline in neurocognitive function as measured by the neurocognitive composite score of the MCCB after 12 weeks of treatment. The MCCB scoring system provides a standardized score for each of the tests in the battery, with a mean score of 50, standard deviation (SD) of 10, and a range of possible scores from 10 (− 4 SD) to 90 (+ 4 SD) [36]. The neurocognitive score was selected because it excludes the social cognition domain, which is typically targeted by separate training procedures. Patients' MCCB performance will be assessed both at screening and at randomization, as changes between the first two assessments have been shown to predict subsequent treatment-related changes [37]. Secondary endpoints include change from baseline after 12 weeks in cognitive function as measured by the overall MCCB composite score, the effect of cognitive deficits on day-to-day functioning as measured by the SCoRS total score, PANSS total score, and the percentage of patients with any AEs or serious AEs (SAEs). Additional PANSS sub-scores, as well as other assessments on SCoRS or Clinical Global Impressions-Severity (CGI-S) will also be evaluated. Novel endpoints include change from baseline in the Balloon Effort Task (BET) score and Virtual Reality Functional Capacity Assessment Tool (VRFCAT) time to completion, number of errors and forced progressions after 12 weeks of treatment.

BET is a computerized, objective task that assesses reward-based decision making, evaluating how much effort the patient is willing to exert for a variable monetary reward [38]. To complete each task, the participant decides whether to take an easy option for a low reward or a harder option for a higher reward. On commencing the test, the participant is shown the potential reward associated with each task and chooses which one to complete. VRFCAT is a computerized virtual reality shopping trip developed to detect functionally meaningful improvements in patients' everyday lives [39, 40]. Outcomes will help to evaluate whether any improvements in neurocognition resulting from an augmentation approach manifest transfer to improvements in functional performance.

As a further endpoint, the novel Patient Reported Experience of Cognitive Impairment in Schizophrenia (PRECIS) instrument will be used in English-speaking patients to assess patients' subjective experiences of CIAS [41]. PRECIS will be administered before MCCB, so that performance on MCCB does not influence responses to the PRECIS questionnaire.

Table 1 Study endpoints

Primary endpoint
Change from baseline in neurocognitive function as measured by the neurocognitive composite score of the MCCB after 12 weeks of treatment
The neurocognitive score includes all MCCB domains except social cognition
Secondary efficacy endpoints
Change from baseline in cognitive function as measured by the overall MCCB score after 12 weeks of treatment
The overall score includes all MCCB domains
Change from baseline in the effect of cognitive deficits on day-to-day functioning as measured by the SCoRS after 12 weeks of treatment
SCoRS is a 20-item interview-based assessment of how cognitive deficits affect day-to-day functioning
Change from baseline in PANSS total score after 12 weeks of treatment
PANSS will be used to evaluate broad psychopathology associated with schizophrenia disease state
Further efficacy endpoints
Change from baseline in each of the 7 MCCB domain scores after 12 weeks of treatment
Change from baseline in PANSS Positive Symptom Scale after 12 weeks of treatment
Change from baseline in PANSS Negative Symptom Scale after 12 weeks of treatment
Change from baseline in PANSS Emotional Expression and Emotional Experience Subscales after 12 weeks of treatment
Change from baseline in CGI-S score after 12 weeks of treatment
CGI-S is a one-item evaluation completed by the clinician to measure the severity of the patient's psychopathology
Change from baseline in BET scores after 12 weeks of treatment
The BET is a computerized task that assesses the patient's willingness to exert effort for reward
PRECIS score (in English-speaking patients only)
PRECIS is a novel patient-reported instrument developed to record patients' subjective experience of CIAS, and the results of this study will support the validation of this outcome measure
Change from baseline in VRFCAT time to completion, number of errors, and forced progressions after 12 weeks of treatment
The VFRCAT is a computerized virtual reality shopping trip developed to detect functionally meaningful improvements in patients' everyday lives, and outcomes
will help to evaluate whether an augmentation approach translates to improved functional performance
CCT performance after 12 weeks will be measured using a global progression scale, which is an average of the level of progression across each exercise
Safety endpoints
Percentage of patients with AEs and SAEs
Including clinically relevant abnormalities identified in physical examination, vital signs, ECG, and laboratory tests
Occurrence of protocol specified AESI
Worsening of disease state as assessed by PANSS
Suicidality as assessed by C-SSRS
Pharmacokinetic endpoints
Pre-dose/trough plasma concentrations of BI 425809 at Visits 3, 4, 5, and 6
To measure study drug compliance

AEs adverse events, *AESI* adverse event of special interest, *BET* Balloon Effort Task, *CCT* computerized cognitive training, *CGI-S* Clinical Global Impressions-Severity, *CIAS* cognitive impairments associated with schizophrenia, *C-SSRS* Columbia Suicide Severity Rating Scale, *ECG* electrocardiogram, *MCCB* Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery, *PANSS* Positive and Negative Syndrome Scale, *PRECIS* Patient Reported Experience of Cognitive Impairment in Schizophrenia, *SAEs* severe adverse events, *SCoRS* Schizophrenia Cognition Rating Scale, *VRFCAT* Virtual Reality Functional Capacity Assessment Tool

2.4 Computerized Cognitive Training

Compliance with CCT will be assessed through a 2-week CCT run-in during the screening period prior to randomization. During the CCT run-in, the target for each patient is ≥ 2 h of CCT per week, for a total of 4 h over 2 weeks. This will identify and exclude patients who are most likely to be non-compliant with self-administered CCT exercises. Compliant patients will be eligible for randomization, and during the 12-week treatment period will complete approximately 30 h of adjunctive self-administered CCT. This target was selected based on the findings of a previous meta-analysis of cognitive training studies in patients with schizophrenia, which showed small-to-medium effect sizes on global cognition of cognitive remediation training with a mean total treatment duration of 32.2 h [12]. It is recommended that patients complete approximately 2.5 h of CCT per week across three to five sessions of 30–50 min each.

Sessions should preferably last ≥ 10 min and not exceed 1 h, to prevent patient fatigue. Minimum compliance with CCT during the treatment period is ≥ 1 h per week, and a protocol deviation will be recorded if a patient completes < 1 h in a given week. CCT sessions will consist of various exercises delivered via the same self-administered program in both the CCT run-in and treatment periods. The CCT program consists of computer-based exercises developed by HappyNeuron Pro (Campbell, CA, USA) to stimulate cognitive functioning in the clinical rehabilitation of patients with schizophrenia. The exercises selected for the study are taken from standard cognitive remediation programs for schizophrenia, in particular the CR-Psychiatry program available through the HappyNeuronpro.com website. A variety of exercises will be delivered so that each patient has limited exposure to any one exercise. In total, the CCT program used in this study consists of 22 exercises, which were selected to train major cognitive functions often impaired in patients with schizophrenia, including processing speed, selective attention, working memory, visual memory, verbal memory, and executive functions. All exercises start at the lowest level of difficulty, and the CCT program then automatically adjusts the level of difficulty to keep patients challenged while minimizing frustration. For this clinical trial, additional content (specifically animations and questionnaires) have been added to the existing HappyNeuron Pro training program to increase engagement for patients who will be completing their training exercises independently at home. A system of rewards, as well as feedback on results (i.e. exercise performance) will also help to motivate patients to complete CCT exercises to target.

A trial site staff member will act as the CCT coach and be responsible for working with patients to ensure adequate compliance with the self-administered CCT exercises. They will provide patients with a device to access the HappyNeuron Pro platform if the patient is unable or unwilling to use their own device. The CCT coach will have access to an online portal to remotely monitor the patient's completion of CCT exercises and will follow-up with patients weekly to provide encouragement and resolve any issues with the CCT program.

2.5 Statistical Analysis

2.5.1 Sample Size Calculation

Monte Carlo simulations (10,000 simulations) were made to assess the probabilities of observing different effect sizes of BI 425809 over placebo, given the true effect sizes. Based on the simulation results, a sample size of 200 patients is sufficient to achieve the aims of this exploratory trial. Predicting a 10% dropout rate, this will result in a total of 180 evaluable patients, or 90 evaluable patients per treatment arm. If the true effect size (mean treatment difference/SD) is 0.45, there is a 64% probability that a mean difference between the treatment and placebo groups greater than 0.4 will be observed, and an 84% probability that a mean difference of at least 0.3 will be seen. On the other hand, assuming the true effect size is only 0.2, there is a 75% probability of observing a mean difference less than 0.3, and a 91% probability of observing a mean difference of at most 0.4. The simulations were performed using R version 3.3.2.

2.5.2 Patient Analysis Sets

There are four patient analysis sets defined in this trial. The randomized set (RS) includes all patients who provided informed consent and were randomized to receive either BI 425809 or placebo on top of CCT. The treated set (TS) includes all patients in the RS who were treated with at least one dose of the trial regimen (including both drug and CCT), and is used for demographics, baseline characteristics, and safety analyses. The full analysis set (FAS) includes all patients in the TS who had non-missing baseline and at least one non-missing post-baseline on-treatment measurement on the primary efficacy endpoint. The FAS will be used for efficacy analyses. The restricted FAS (FAS compliance) includes all patients in the FAS who are compliant with both the trial medication and CCT. It will be used for sensitivity analyses of the primary efficacy endpoint. In both the FAS and the restricted FAS, patients will be analyzed as randomized.

2.5.3 Primary Analysis of the Primary Endpoint

The primary analysis of the primary efficacy endpoint will be performed on the FAS. The restricted maximum likelihood-based mixed model for repeated measures (MMRM) will be utilized, using full information procedures fitted for change from baseline in the MCCB neurocognitive composite score after 12 weeks of treatment. The MMRM model will include continuous baseline MCCB neurocognitive composite score and change in MCCB neurocognitive composite score from screening to baseline as covariates, treatment, age stratification factor (≤ 40 years vs > 40 years) and visit as factors, as well as treatment-by-visit and baseline-by-visit interactions. Patients will be treated as random effect. The unstructured variance–covariance structure will be used to model the within-patient variability and the Kenward–Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using SAS PROC MIXED procedure. The primary treatment comparisons will be the contrasts between treatment groups (BI 425809 + CCT vs placebo drug + CCT) at Week 12. All p values will be

considered descriptive; 95% confidence intervals (CI) will also be provided.

2.5.4 Sensitivity Analyses of the Primary Endpoint

The same MMRM model as used for the primary analysis of the primary endpoint will be used on FAS compliance as sensitivity analysis for the primary efficacy endpoint. Additional sensitivity analyses of the primary endpoint will be conducted on the FAS, using an analysis of covariance (ANCOVA) model that includes treatment and age (≤ 40 years vs > 40 years) as factors, and baseline and/or change from screening to baseline in MCCB neurocognitive composite score as a continuous covariate. Last observation carried forward will be used to impute missing values at Week 12.

2.5.5 Secondary Endpoint Analyses

The analyses of efficacy-related secondary endpoints will be performed on the FAS. The same model used for the primary analysis of the primary endpoint will be used on change from baseline in the MCCB overall composite score. The secondary endpoint of change from baseline in PANSS total score after 12 weeks of treatment will be analyzed using an MMRM model that includes treatment, age and visit as factors, the corresponding baseline value as a covariate, and treatment-by-visit and baseline-by-visit interactions. For change from baseline in SCoRS score after 12 weeks of treatment, an ANCOVA model that includes treatment and age as factors and its corresponding score at baseline as a covariate will be fitted. The adjusted mean values and the treatment group contrasts at Week 12 will be presented together with the 95% CIs. All *p* values will be considered descriptive. For the percentage of patients with SAEs (including clinically relevant abnormalities of physical examination, vital signs, electrocardiogram [ECG], and laboratory tests), comparison will be made for BI 424809 + CCT group versus placebo + CCT group on TS together with descriptive statistics. For other secondary endpoints, only descriptive statistics and exploratory analyses will be provided.

2.5.6 Further Endpoints Analyses

Further efficacy endpoints will be analyzed using MMRM/ANCOVA. Additional exploratory analyses may be performed as appropriate, depending on the outcome of the trial, including predictors of changes in the VRFCAT in the event that such changes are detected.

3 Discussion

This large, international trial of BI 425809 with self-administered CCT over 12 weeks aims to evaluate whether BI 425809 pharmacotherapy on top of a background of increased cognitive stimulation delivered through self-administered CCT is beneficial in improving neurocognitive and functional outcomes in patients with schizophrenia. Previous studies in healthy volunteers have demonstrated that BI 425809 10 mg is well tolerated and increases glycine levels in cerebrospinal fluid after multiple doses [28, 31].

Pharmacological augmentation of cognitive training approaches has been explored using agents such as psychomotor stimulants (e.g. amphetamine and methylphenidate), the alertness-promoting agent modafinil, and glutamatergic modulators (e.g. D-cycloserine and D-serine), and these approaches have been reviewed previously [19]. These approaches have primarily been tested in smaller and shorter trials, which have varied in terms of trial design and outcomes. Some trials have reported improvements in cognitive task performance, but they have not typically translated to improvements on untrained tasks. The largest and longest study to date to combine pro-cognitive pharmacotherapy with CCT, used drugs that enhance NMDA/neuroplasticity and randomized 104 patients with schizophrenia to 12 weeks of D-serine, an endogenous ligand at the NMDA receptor glycine binding site, or placebo. However, this treatment did not lead to significant improvements in global cognition or functioning [15]. In a double-blind study of 40 patients with schizophrenia, who received D-cycloserine or placebo once weekly for 8 weeks alongside a CCT program, auditory processing speed was improved, but this improvement did not translate to untrained tasks [16]. In contrast, among 28 patients with schizotypal personality disorder, patients receiving daily treatment with the α_{2A}-adrenergic receptor agonist guanfacine on a background of CCT and social skills training over 8 weeks, showed greater improvement on MCCB reasoning, problem-solving domains and University of California San Diego Performance-Based Skills Assessment total score than patients receiving only CCT and social skills training [20].

Two double-blind trials have explored combinations of CCT approaches with the wakefulness-promoting drug modafinil. A trial in 49 patients with schizophrenia receiving modafinil or placebo once daily for 10 days revealed no significant effects on neuropsychological, functional, and clinical measures [17]. In the second trial, 33 healthy volunteers received modafinil or placebo once daily over a 10-day period of cognitive training. Modafinil improved trained language learning task performance, but these improvements did not generalize to improvements in MCCB score [42]. A double-blind crossover study of 35 healthy volunteers and 25

patients with schizophrenia reported improvements in auditory processing speed 1 week after a single dose of amphetamine on a background of cognitive training [18]. However, it may be that treatment with psychomotor stimulants and related drugs such as modafinil could increase attention and cognitive task performance through increased motivation to engage in such tasks [19]. Based on these studies, it remains unclear whether increased cognitive stimulation through CCT approaches can increase the efficacy of plasticity-promoting or stimulant drugs in improving neurocognition.

The trial described in the present paper includes several novel design features intended to generate robust data and provide a clear indication of whether augmentation of BI 425809 pharmacotherapy with CCT can improve neurocognitive and functional outcomes in patients with schizophrenia. The trial aims to recruit 200 patients, and as such will be larger than any of the previous trials described above. Furthermore, this trial employs a strategy of daily dosing over 12 weeks. Since motivation is likely to be an important factor in the success of this trial, the BET will be used to monitor patients' motivation and to explore the role of effort in neurocognitive and functional outcomes, as well as engagement with the CCT program. The computer-based CCT program used in this study offers a number of advantages over other non-computerized approaches, including an extensive range of multisensory training possibilities with rapid feedback and personalization [14]. CCT can also be consistently delivered in the patient's home setting, which is more convenient for patients who may have difficulty accessing cognitive training programs in the clinic. This trial will investigate the effect of a combined pharmacological intervention with self-administered CCT and will demonstrate whether this approach can be effectively implemented in a large multicenter trial across several countries. Additionally, the use of the PRECIS instrument in a subset of patients will provide the patient perspective on any improvement in cognitive and functional outcomes [41]. Finally, this trial will use functional assessments including the interview-based SCoRS questionnaire as well as the novel VRFCAT to evaluate performance on untrained day-to-day functional skills, to explore the degree to which neurocognitive gains transfer to improvements in everyday functional performance.

4 Conclusions

This trial will determine the benefit of combining BI 425809 pharmacotherapy with cognitive stimulation through self-administered CCT in patients with schizophrenia. Additionally, the trial will evaluate whether improvements in neurocognition translate into improved everyday functioning, whether self-administered CCT can be effectively implemented in a large multinational trial, and the role of motivation in neurocognitive and functional improvements.

4.1 Trial Status

This trial (protocol version 1.0, 13 September 2018) was registered on Clinicaltrials.gov on March 1, 2019 (NCT03859973). The trial was initiated in April 2019 and recruitment, which is currently ongoing, began in June 2019. The last patient out is planned for December 2020 and results are expected in early 2021.

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Author Contributions All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted. PDH and CRB assisted in the design of the trial and consulted on its methodology. SM is the clinical trial leader. JP is the leader of the BI 425809 clinical development program and designed the trial and its methodology.

Compliance with Ethical Standards

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Conflict of interest PDH has received consulting fees or travel reimbursements from Alkermes, Boehringer Ingelheim, Intra Cellular Therapies, Otsuka America, Roche, Sanofi Pharma, Sunovion Pharma, Takeda Pharma, and Teva Pharma during the past year. He has a research grant from Takeda and from the Stanley Medical Research Foundation. SM is an employee of Boehringer Ingelheim (Canada) Ltd. JP is an employee of Boehringer Ingelheim International GmbH. CRB has received consulting fees from Boehringer Ingelheim, Pfizer, and Lundbeck. He has research funding from Takeda, Lundbeck, and Pfizer, and has received in-kind research user accounts from Scientific Brain Training Pro.

Ethics Approval The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH-GCP, relevant Boehringer Ingelheim Standard Operating Procedures, and other current relevant regulations and has been approved by the local ethics committees of all participating study sites.

Informed Consent Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and to the regulatory and legal requirements of the participating country.

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