Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000115: EPICOG-SCH
Letter of Intent

Administrative Structure:

Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information not contained within the cover letter.

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Concept(s) of Interest (COI) for Meaningful Treatment Benefit:

A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of symptoms, limitations in performance of daily activities).

Cognitive impairment in Schizophrenia (CIAS) is one of the primary features of the disorder and it has been associated to an impact on patient functioning in daily life (Bowie and Harvey, 2006; Harvey et al., 2014; et al, Green, et al. 2015). Overall, cognition accounts for 20–60% of the variance in patients' functional outcomes depending on the studies and methods used to measure both factors (Galderisi et al., 2014; Velligan et al., 1997; Zaragoza Domingo et al., 2015).

Within last decade, treatment of CIAS has been one of the most important targets in schizophrenia management, together with functional rehabilitation. During last decade, patient´s functionality was recognized as one of the main clinical endpoints for Schizophrenia management, together with symptom control WFSBP (World Federation of Societies of Biological Psychiatry) & APA (American Psychiatric Association) (Hasan et al., 2012; Lehman et al., 2010). The International Society for CNS Clinical Trials and Methodology (ISCTM) in several meetings of experts reached consensus on several important issues for CIAS drug development; in the meeting held on 2014 it was concluded that cognitive impairment and functional disability were viewed as equally important treatment targets (Buchanan et al., 2011; Kefee et al., 2016).

In spite of the efforts, although some new compounds look promising, **no treatments have been proven available to treat cognition** in clinically stable schizophrenia patients. Nowadays, available treatments for psychosis allow patients have control over delusions and other psychotic symptoms; however cognitive disturbances are still present with different prevalence values and severity depending on the measured cognitive domain.

In outpatients clinical settings, up to a 78% of patients expressed to suffer cognitive disturbances following an open question (Zaragoza Domingo et al., 2017). For instance, patients expressed difficulties conducting daily activities as reading a book, following a conversation, handling administrative domestic duties and remembering items when shopping, among others.

Based on objective evaluation, Zaragoza Domingo (2015) described the **prevalence of cognitive disturbances** in a comprehensive study involving a large sample of patients in Spain (Europe). Results from this cross-sectional project showed that the prevalence of cognitive dysfunction was as much high as 68% for Executive Functioning, 38% for Information Processing Speed, 25% for Verbal Memory and 21% for Working Memory. These results, confirmed also a marked heterogeneity in terms of the number of domains impaired (performance set at <1.5 SD cut-off) and its severity. In this line, while an important part of patients showed impairment in one single domain (41%) others showed impairment in two (30%) three (12%) or four domains (9%). Few patients, a 6%, showed performance within normal ranges across all measured cognitive domains. Other published studies, also have documented that among schizophrenia patients it can be found a range of 20-25% of patients with a level of performance as healthy population depending on the studied cognitive domain (Lennertz et al., 2016).

In a recent published research conducted in clinically stable outpatients, **cognitions contribution to overall functionally** as measured as disability by WHO-DAS-S was around 18%, reaching almost a 50% when including other relevant with other clinical and sociodemographic factors (Zaragoza Domingo et al., 2015).

The difficulty to **translate changes on cognitive performance into a measurable impact in patient daily life** is recognized in several CNS diseases. However, in schizophrenia, the contribution of cognition over functionality, has been the aim of many research programs, and across studies it is quite well described how functional capacity bridges cognition with everyday life skills (Galderisi et al., 2018).

Therefore, any treatment aiming to improve cognition would, in turn, have a potential impact on patient´s functioning in daily life. Improvements in cognition, should ameliorate patient´s limitations in daily life making the patient´s feeling more competent in different life dimensions i.e. areas as self-care, social, work, home, et. In this context, it is important to highlight that given its chronic nature, any change on functionality would need several weeks/months to take place and probably the length of clinical trials does not allow this to arise.

Both factors cognition and functionality are measured in clinical trials for new treatments on CIAS, usually as independent factors but not combined in a single measure. To have such combined measure would be a clear advantage for clinical endpoints in CIAS indication.

Provide a conceptual framework for the COA(s)

Given the heterogeneity of cognitive disturbances overserved in schizophrenia samples, the new COA, EPICOG-SCH is built to be a **brief** instrument useful for screening of cognitive health, in order to **identify** cognitive impairment of core symptoms in clinically stable patients and useful to **quantify** its severity. Due to its brief nature, the battery is limited to evaluate the core and the most prevalent impaired domains in this disorder, setting level of severity.

Classical neuropsychological test are well known among Mental Health professionals and communities of clinical neuroscientists all over the world. Furthermore, classical tests have the advantage to be already available in many languages and to have available normative data in a large number of countries in the world.

The new COA, the EPICOG-SCH is composed by 4 very well known classical neuropsychological subtests with two main purposes; first, **to understand** patient performance for each subtest compared to different reference populations (local normative population and from schizophrenia sample population) and second, **to quantify** the overall cognitive performance by calculating summary composite scores as an indicator of global cognitive health.

As for the first purpose, the availability of **population-based normative data** allows to identify for each patient those domains that are impaired compared to country population considering or not, sociodemographic adjustment factors. For the second purpose, to have a specific large **schizophrenia normative database**, also allows to understand patient´s performance compared to a country-representative sample of patients with the same diagnostic based either on each individual subtests and based on summary composite scores.

EPICOG-SCH has two summary Composite Scores validated in stable schizophrenia patients, one is build based on the **unitary sum** of all subtests of the battery (UCS) and a second Composite Score, build upon **an algorithm** that combines cognitive results with a measure of functional disability (FWCS).

The **Functional Composite Score** brings a new information to clinicians, about the potential for an independent life based on patient´s cognitive status. The development of the EPICOG-SCH Functional Composite Score was based in an innovative algorithm, and any effect observed on this Functional Composite Score will involve a variation on patient´s independent life mediated by cognitive health.

Existing approved COAs instruments i.e. **MATRICS MCCB** (Green et al., 2004)) although is broadly comprehensive regarding the coverage of cognitive dimensions, also require **long administration** times impacting on patient´s performance due to fatigue produced by testing burden.

Also, MCCB involves the measurement of a larger number of dimensions than EPICOG-SCH, performance is combined in a single Composite Score which might dilute the effects produced by any intervention at least over the key core domains (Executive Functioning, Information Speed and Memory dimensions).

The new COA, EPICOG-SCH can be an alternative to MBCC, in terms of brevity, also because includes only classical tests already existing in clinical practice around the world and adding the innovative validated algorithm related to patient´s functional independence. In addition, for **Executive Functioning** evaluation i.e. CFT the EPICOG-SCH battery includes 3 subtests with different levels of difficulty i.e. animals versus fruits compared to MBCC that includes only one item (Animals).

Context Of Use for COA Qualification:

Targeted study population including a definition of the disease and selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups).

The context of use of EPICOG-SCH is in clinical trials of new compounds targeting treatment of CIAS in clinically stable schizophrenia patients.

In this context, the battery has three main applications:

1- To measure symptom severity as ***cognitive clinical endpoint***, administering the battery at baseline and at after study drug treatment completion.

2- To identify ***cognitive impairment*** among study patients based in an objective measurement. This can be reached by administering the battery as a screening instrument in clinical trials either for sample selection, sample enrichment in terms of cognitive impairment, or sample stratification.

3- To identify patients with an ***optimal level of cognitive health*** allowing a minimal functional independent life. This can be reached by administering the battery at different time points and calculating the number of patients reaching a specific validated cut off score for the FWCS(>96), and comparing the percentage among active new investigational drug versus placebo or active standard treatment.

Selection Criteria for each application

Application 1 – Endpoint for CIAS Severity - Anticipated Selection Criteria for Clinical Trials

Inclusion Criteria:

- Male and/or female subjects between the ages of 18 and 50 years, inclusive, with Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnosis of schizophrenia of at least 2 years duration
- Subjective complaints for cognitive impairment or moderate cognitive impairment as measured by Clinician´s based impression scale CGI-SCH-S Cognitive Symptoms score ≥ 4 (Haro et al., 2003).
- Evidence of stable schizophrenia symptomatology >=3 months (ie, no hospitalizations for schizophrenia, no increase in level of psychiatric care due to worsening of symptoms of schizophrenia).
- Subjects in ongoing maintenance atypical antipsychotic therapy, on a stable treatment regimen for >=2 months prior to Baseline/Day 1, including concomitant psychotropic treatments and anticholinergic agents to treat extrapyramidal symptoms.
- Subject must have an identified informant
- Subject must reside in a stable living situation for at least 12 weeks prior to Screening.
- Patients able to understand testing instructions and adequately corrected if any sensorial deficit is present available the time of cognitive evaluation (glasses or any other corrector device).

Exclusion Criteria:

- Subjects with a current DSM-5 diagnosis of schizoaffective disorder in the judgment of the investigator.
- Subjects with a current DSM-5 diagnosis of major depressive episode, manic and hypomanic episode, panic disorder, agoraphobia, social anxiety disorder, obsessivecompulsive disorder, post-traumatic stress disorder, generalized anxiety disorder using based on standardized instruments.
- Subjects with a lifetime DSM-5 diagnosis of antisocial personality disorder, anorexia nervosa, bulimia nervosa, binge-eating disorder based on standardized instruments.
- Subjects who meet the DSM-5 diagnosis of moderate or severe psychoactive substance use disorder (excluding nicotine dependence) within 12 months of screening.
- Subjects with significant extrapyramidal symptoms which have not been stabilized with anticholinergics.

Application 2, 3 - Anticipated Selection Criteria for Clinical Trials with a Selection of Patients with <u>Evidences</u> of Cognitive Impairment or Stratification factor.

Patient Selection will be the same as Application 1 but including one of the following criteria (to be decided based on the study drug mechanism of action):

- Patients with cognitive impairment at least in two cognitive domains based on country normative samples for specific tests included in EPICOG-SCH battery (subtest test result < 1.5 SD) or if only one domain it is a working memory test.
- Patients with prominent cognitive impairment based in both, subjective complaints and evidenced by objective measurement with a result of EPICOG-SCH UCS below -1.SD (< 85).
- Patients with prominent cognitive impairment impacting in real life based in subjective complaints and evidenced by objective measurement with a result of EPICOG-SCH FWCS cut off score < 96.

***Targeted study design and statistical analysis plan (includes the role of the planned COA in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate*).**

Targeted study design for the treatment of Cognitive Impairment Associated to Schizophrenia is a Randomized, Double-blind, Placebo Controlled, Parallel Group Study of 12 weeks of New Drug treatment.

Primary Outcome Measures:

1. Change on functional prognostic factor measured as a change From Baseline in the EPICOG-SCH FWCS to week 12 [Time Frame: Screening, Baseline, Week 6, Week 12]

Secondary Outcome Measures:

1. Change on core schizophrenia cognitive health as measured as change from Baseline in the EPICOG-SCH UCS to week 12 [Time Frame: Screening, Baseline, Week 12]
2. Change on cognitive profiles as measured as a change from Baseline in the EPICOGSCH Indexes to week 12 [Time Frame: Screening, Baseline, Week 12]
3. Change on cognitive specific domains as measured as a change from change from Baseline in the EPICOG-SCH subtests to week 12 [Time Frame: Screening, Baseline, Week 12]
4. Change on clinician´s based impression of severity of cognitive symptoms from Baseline in the CGI-SCH Cognitive Score (Clinical Global Impression-Severity for Cognitive Score) to Week 12 [Time Frame: Screening, Baseline, Week 2, Week 6, Week 12]
5. Cognitive-functional remission as the number of patient reaching a functional score of functional independence in daily life, i.e. cut-off score for FWCS (cut-off < 96).

Applicable study settings for future clinical trials

- ***Geographic location with language/culture groups***

Subtests composing the EPICOG-SCH battery are classical measures broadly known by psychologists, neuropsychologists and psychiatrists i.e. Mental Health professionals, and available in multiple languages in the world. This is because 3 out 4 the subtests of the battery came from Wechsler batteries (WAIS and WMS 3rd Edition) which already translated into multiple languages and commercialized in multiple countries as in US (Wechsler, 1997; Wechsler, 1997) and Spain (Wechsler, 2001; Wechsler, 2001). The way the tests are used in the EPICOG-SCH are the same as suggested in the original test manuals regarding administration, recording and scoring rules. The fourth test of the battery, is also part of a well known battery with minimal changes in the instructions Delis-Kaplan Executive Function System D-KEFS Verbal Fluency condition category fluency, also already existing in clinical practice (Dean et al., 2001). For this last subtest, subtle modifications on the category selected should be done in advance on each country before its application, based on normative data to ensure similar degree of word production (for instance to move from Vegetables to Fruits) as the categories to be selected on each country should be set following a review of local validation literature.

In summary, the test itself can be applied in **all countries and culture groups.** However, it is anticipated that the prognostic FWCS will require pre-calibration on each country in order to set the weights composing the algorithm to cultural specificities related to mental health care with the society.

- ***Other study setting specifics (e.g., inpatient versus outpatient)***

So far EPICOG-SCH has been validated for its use in outpatient settings with stable clinical picture. During acute periods, cognition could have a different clinical picture with broad variations in short periods of time ie. days or weeks, and also variations due to drug titration post-acute periods. Therefore, for its use and value during inpatient periods its utility should first conduct a clinical validation which is not done so far by the author.

COA Type: PerfO

References:

Bowie, C. R. & Harvey, P. D. (2006). Cognitive deficits and functional outcome in schizophrenia. Neuropsychiatr.Dis.Treat., 2, 531-536.

Buchanan, R. W., Keefe, R. S., Umbricht, D., Green, M. F., Laughren, T., & Marder, S. R. (2011). The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive enhancing drugs: what do we know 5 years later? Schizophr.Bull., 37, 1209-1217.

Dean C. Delis, Edith Kaplan & Joel H. Kramer, Delis Kaplan Executive Function System (DKEFS) (2001), The Psychological Corporation, San Antonio, TX.

Green, M. F. & Nuechterlein, K. H. (2004). The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr.Res., 72, 1-3.

Green, M. F., Llerena, K., & Kern, R. S. (2015). The "Right Stuff" Revisited: What Have We Learned About the Determinants of Daily Functioning in Schizophrenia? Schizophr.Bull., 41, 781-785.

Galderisi, S., Rossi, A., Rocca, P., Bertolino, A., Mucci, A., Bucci, P. et al. (2014). The influence of illness-related variables, personal resources and context-related factors on real-life functioning of people with schizophrenia. World Psychiatry, 13, 275-287.

Galderisi, S., Rucci, P., Kirkpatrick, B., Mucci, A., Gibertoni, D., Rocca, P. et al. (2018). Interplay Among Psychopathologic Variables, Personal Resources, Context-Related Factors, and Real-life Functioning in Individuals With Schizophrenia: A Network Analysis. JAMA Psychiatry, 75, 396-404.

Haro, J. M., Kamath, S. A., Ochoa, S., Novick, D., Rele, K., Fargas, A. et al. (2003). The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl, 16-23.

Harvey, P. D. (2014). What is the evidence for changes in cognition and functioning over the lifespan in patients with schizophrenia? J.Clin.Psychiatry, 75 Suppl 2, 34-38.

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F. et al. (2013). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J.Biol.Psychiatry, 14, 2-44.

Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O. et al. (2010). Practice guideline for the treatment of patients with schizophrenia, second edition. Am.J.Psychiatry, 161, 1-56.

Lennertz, L., An der, H. W., Kronacher, R., Schulze-Rauschenbach, S., Maier, W., Hafner, H. et al. (2016). Smaller than expected cognitive deficits in schizophrenia patients from the population-representative ABC catchment cohort. Eur.Arch.Psychiatry Clin.Neurosci., 266, 423-431.

Keefe, R. S., Haig, G. M., Marder, S. R., Harvey, P. D., Dunayevich, E., Medalia, A. et al. (2016). Report on ISCTM Consensus Meeting on Clinical Assessment of Response to Treatment of Cognitive Impairment in Schizophrenia . Schizophr.Bull., 42, 19-33.

Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, A. L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. Schizophr.Res., 25, 21-31.

Wechsler D (1997). Wechsler Adult Intelligence Scale. (Third Edition ed.) San Antonio TX: The Psychological Corporation.

Wechsler D (1997). Wechsler Memory Scale. (Third Edition ed.) San Antonio TX: The Psychological Corporation.

Wechsler D (2001). Escala de Memoria de Wechsler para Adultos: Manual de Aplicación y Corrección. Madrid: TEA Ediciones.

Wechsler, D. (2001). Escala de Inteligencia de Weschler

Zaragoza Domingo, S., Bobes, J., García-Portilla, M., & Morralla, C. (2015). Cognitive Performance Associated to Functional Outcomes in Stable Outpatients with Schizophrenia. Schizophr.Res.Cogn, 2, 146-158.

Zaragoza Domingo, S., Bobes, J., García-Portilla, M., & Morralla, C. (2017). EPICOG-SCH: A brief battery to screen cognitive impact of schizophrenia in stable outpatients. Schizophr.Res.Cogn, 8, 7-20.