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Title: Assessing the value of an AI Platform during the screening period to evaluate and predict adherence to study drug intake during treatment in an ongoing proof of-concept phase 2 study in schizophrenia

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Methodological questions being addressed: Minimizing subject non-adherence is critical to clinical trials, in particular in proof-of-concept studies which aim to show preliminary evidence of efficacy in a relatively small sample size of a clinically relevant population. Can adherence to placebo dosing during screening be used as an accurate predictor of adherence post-randomization?

Word Count: 497 (max 500)

Introduction: Non-adherence remains a major challenge in schizophrenia clinical trials and traditional methods to monitor adherence such as pill count and self-report are not deemed sufficiently reliable. Accurately monitoring and collecting drug adherence data can allow for a better understanding of drug effects and increase the quality of the data collected. Here, we report on the utility of using an Artificial Intelligence (AI) platform to monitor and increase adherence to study treatment in an ongoing Phase 2b study of basmisanil for the treatment of Cognitive Impairment Associated with Schizophrenia (BP39207). We assess the added value of incorporating the AI Platform during the screening phase in order to identify putative non-adherent patients during the treatment phase.

Methods: Subjects were randomized to a 24-week double-blind placebo-controlled treatment phase, following a 5-week screening period which included a 1-week placebo dosing "try-out phase". Subjects are asked to dose using the AI application on a smartphone, from try-out phase on and throughout the 24 weeks of treatment. The adherence measure is based on AI platform adherence data, obtained by visual recognition and confirmation of drug ingestion by the patient.

We performed an analysis of predictive validity, to determine whether adherence rates during try-out predict adherence rates during study treatment and if so, which thresholds can be used to most accurately predict non-adherence (positive target) behaviors.

Results: So far, 94 subjects have been randomized. N=92 subjects, receiving at least 1 dose of the study drug had available average cumulative dose adherence values during both try-out and treatment periods, were

included in the analysis. Average adherence for try-out and treatment periods were 91% and 83% respectively. We tested different thresholds to define "adherence to treatment", i.e. ≥70%, ≥80% and ≥90% of doses correctly taken. The different thresholds allowed for the correct identification of 95 to99% of all compliant subjects, demonstrating high specificity. On the other hand, adherence during try-out demonstrated low sensitivity across thresholds (15 to 41%), indicating that only a small fraction of non-compliers could be readily identified during screening. The probability that the identified subjects remained non-adherent during the treatment period differed between thresholds, with more stringent thresholds yielding higher positive predictive values (from 0.63 to 0.95). Using the AI platform to monitor study drug intake during a try-out phase and setting a threshold of >90% adherence led to the correct identification of 98% of compliant subjects post-randomization with a low false positive rate resulting in high positive predictive value of non-compliance of 0.95.

Conclusions: Incorporating an AI platform during screening period to screen out potential poor compliers could be a valuable tool in mitigating the risks of suboptimal adherence during the treatment phase and thus improve signal-to-noise ratio. The potential introduction of a biais of such methods , their generalizability, as well as next validation steps will be discussed. Our results suggest that it is possible to pre-determine adherence thresholds that could be implemented as part of eligibility criteria to select patients that are most likely to comply to study procedures.

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