Title: Towards a better understanding of informant contributions to schizophrenia trial quality: data from the encenicline cognitive impairment program.

Authors: Nations KR[1], Rosenthal AS[1], Spiridonescu L[1], Truskowski L[1], Quintanilla A[1], Prilliman C[1], Wise-Rankovic A[1], Gibertini M[1], Brannan S[2], Hilt DC[2]

[1]INC Research, [2]FORUM Pharmaceuticals

The Methodological Question Being Addressed: What definition of a "reliable informant" in a schizophrenia protocol is most likely to optimize trial quality and signal detection?

Introduction: Schizophrenia protocols often require eligible subjects to bring a reliable informant in order to inform medical/symptomatic history. However, definitions of "reliable" vary widely and are often based on clinical intuition rather than actual trial data. The current analysis examined informant characteristics from two Phase 3 trials evaluating 1 and 2 mg encenicline vs placebo for cognitive impairment in schizophrenia (CIS; Potkin et al, 2016), aiming to understand the extent to which these factors predict trial quality and influence treatment effects.

Methods: EVP-6124-015 & 016 were identical, randomized, double-blind, 26-week, multi-national trials that together included 1520 randomized subjects. Neither trial showed a significant treatment effect on co-primary endpoints, which were the MATRICS Consensus Cognitive Battery (MCCB) Neurocognitive Composite Score to measure cognitive performance, and the Schizophrenia Cognition Rating Scale (SCoRS) to measure cognitive functioning. SCoRS collects information from both subject and informant. A "consistent informant" was required for subject entry, defined as a person who interacts with the subject at least twice per week, and who could accompany the subject to site visits. As part of a pre-baseline eligibility review conducted by the CRO medical/clinical team, data were collected on four informant variables: 1) type of relationship to subject (e.g., parent, healthcare professional), 2) duration of relationship with subject (e.g., lifetime, <1 year), 3) type of contact (e.g., intermittent, cohabitating), and 4) weekly time with subject (hours). These factors were evaluated for their ability to predict subject quality, markers for which included trial completion; drug compliance (detectable drug levels at every visit); and non-response to placebo on MCCB (<5 point change from baseline (CFB), SCoRS (<7 points CFB), and CGI-I (>2 at endpoint).

Results: Informant factors reported at screening were not associated with subject/trial quality indicators during the trial, with one exception: type of contact between the subject and their informant significantly predicted trial completion (χ^2=20.01, p<0.001). Of those subjects cohabitating with their informant, 83.3% completed the trial, in contrast to 64.4% of subjects with daily, but not overnight, informant contact (OR = 2.12, 95% CI: 1.5%, 3.2%). Type of contact as a quality predictor was further supported by an important interaction between treatment group and type of contact on the MCCB CFB [F(4,1304)=2.08, p=0.08], showing that in the 2 mg group, but not in the placebo or 1 mg groups, subjects cohabitating with their informant were more improved at endpoint than subjects with daily contact.

Conclusions: Post hoc analysis of informant characteristics showed that type of contact, but not type or duration of relationship, or weekly hours of interaction, was a significant predictor of a subject quality marker (trial completion) in the Phase 3 encenicline program. These data may serve as a source for appropriate and operationally feasible definitions of informant reliability in future CIS protocols. Regional

differences in informant factors and their relationship to subject/trial quality and outcome will be further examined.

References:

Potkin S., Brannan S., Dgetluck, N., Keefe, R.S., Hilt, D.C., and the encenecline CIS Phase 3 study collaborative. *Randomized, double-blind, placebo-controlled, Phase 3 study of encenicline as procognitive treatment in patients with schizophrenia (2016 May)*. Poster session presented at the 169th annual meeting of the American Psychiatric Association, Atlanta, GA.

Disclosures: Funding was provided by FORUM Pharmaceuticals. INC Research was the CRO responsible for execution of both trials. KN, ASR, LS, LT, AQ, CP, AWR, and MG are employees of INC Research. SB and DH were employees of FORUM at the time of this research.