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

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Methodological Question

What definition of a "reliable informant" in a schizophrenia protocol is most likely to optimize trial quality and signal detection?

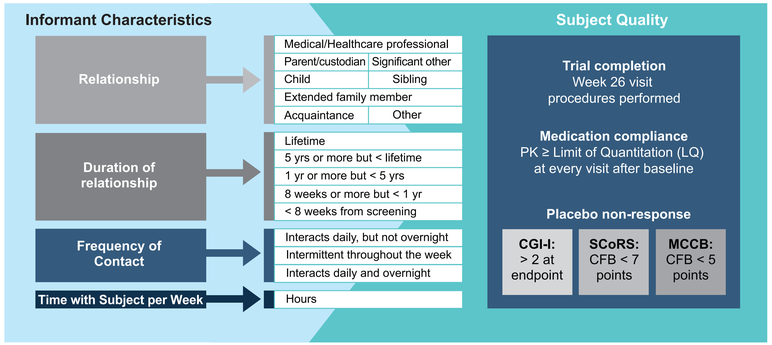
Introduction

Schizophrenia protocols often require eligible subjects to bring a reliable informant in order to inform medical/symptomatic history. In Cognitive Impairment in Schizophrenia (CIS) trials, this is particularly true, given that interview-based assessments named as the functional co-primary endpoint often require both subject and informant input. Recent studies emphasize the importance of reliable informants in order to increase validity of the data (Keefe et al, 2015). However, definitions of "reliable" vary 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 mg and 2 mg encenicline vs placebo for CIS (Potkin et al, 2016) to better understand informant characteristics and 1) how they differ regionally, 2) how they inform subject quality, 3) how they influence the relationship between cognitive performance and functional measures, and 4) whether they impact the primary outcome of the trial.

Methods

- EVP-6124-015 & 016 were identical, randomized, double-blind, 26-week, multi-national trials that together included 1520 randomized subjects. Qualified subjects were diagnosed with schizophrenia and were symptomatically stable and taking an atypical antipsychotic at least 8 weeks before screening.
- Trial co-primary endpoints were the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein and Green et al, 2006) Neurocognitive Composite Score (Green et al, 2014) to measure cognitive performance, and the Schizophrenia Cognition Rating Scale (SCoRS; Keefe et al, 2006) to measure cognitive functioning. Both trials failed to demonstrate an advantage of EVP-6124 over placebo in the co-primary endpoints (Potkin, 2016).
- Due to the SCoRS reliance on informant report, the EVP-6124 protocols required a "consistent informant" 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 characteristics in the interest of verifying eligibility. Characteristics included 1) relationship to subject, 2) duration of relationship, 3) frequency of contact, and 4) hours per week spent with the subject (Figure 1).
- The current analysis examined these informant characteristics and how they influenced markers associated with subject quality, and whether they impacted trial outcome. Selected quality markers are defined in Figure 1.

Figure 1. Informant Characteristics and Subject Quality Markers Defined



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Disclosures

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

Results

Informant Characteristics

- Parents/ custodians made up the largest proportion (45%) of identified informants overall; 61% of subjects had known their informants all their lives. Fully 64% of subjects cohabitated with the named informant (interacting with the subject daily and overnight), and the mean number of interaction hours per week between subjects and their informants was 50.06 (±38.37). Summary statistics of all informant characteristics are presented in Table 1.
- The EVP-6124 studies were conducted in a total of 17 countries in pooled into 4 regions.
  - **North America:** Canada, United States
  - **Europe:** Germany, Great Britain, Italy, Poland, Romania, Russian Federation, Serbia, Spain, Ukraine
  - **Latin America:** Argentina, Brazil, Colombia, Mexico
  - **Asia Pacific:** Australia, Singapore
  - Eight subjects (less than 1% of the overall sample) were recruited in Asia Pacific (Australia and Singapore), and due to lack of interpretability of data associated with this small sample, and based on cultural and standard of care similarities, these eight subjects were pooled with North American subject data for the current analysis.

Table 1. Informant characteristic summary statistics, overall and by region

Informant Variable	NA/APAC (N=783)	EUR (N=550)	LATAM (N=154)	Overall (N=1487)
Relationship Type	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Parent/custodian	239 (30.5)	331 (60.2)	105 (68.2)	675 (45.4)
Significant other	125 (16)	65 (11.8)	14 (9.1)	204 (13.7)
Child	18 (2.3)	25 (4.6)	3 (2.0)	46 (3.1)
Sibling	65 (8.3)	36 (6.6)	13 (8.4)	114 (7.7)
Extended family member	36 (4.6)	23 (4.2)	9 (5.8)	68 (4.6)
Medical/healthcare professional	109 (13.9)	39 (7.1)	4 (2.6)	152 (10.2)
Acquaintance	188 (24.0)	31 (5.6)	6 (3.9)	225 (15.1)
Other	3 (0.4)	0	0	3 (0.2)
Contact Frequency	**N (%)**	**N (%)**	**N (%)**	**N%**
Interacts with subject daily, but not overnight	156 (20.0)	41 (7.5)	8 (5.2)	205 (13.8)
Interacts with subject daily and overnight	416 (53.1)	396 (72)	132 (85.7)	944 (63.5)
Intermittent interaction throughout the week	209 (26.7)	113 (20.6)	14 (9.09)	336 (22.6)
Missing	2 (0.2)	0	0	2 (0.1)
Duration of Relationship	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Lifetime	352 (45.0)	425 (77.3)	131 (85.1)	908 (61.1)
5 years or more but less than Lifetime	179 (22.9)	77 (14.0)	18 (11.7)	274 (18.4)
1 year or more but less than 5 years	188 (24.0)	36 (6.6)	5 (3.3)	229 (15.4)
8 weeks or more but less than 1 year	57 (7.3)	12 (2.2)	0	69 (4.6)
Less than 8 weeks from screening	7 (0.9)	0	0	7 (0.5)
Hours per week with informant	**NA/APAC**	**EUR**	**LATAM**	**Overall**
Mean (SD)	44.44 (38.96)	56.19 (37.80)	56.65 (32.75)	50.06 (38.37)

NA = North America, EUR = Europe, LATAM = Latin America, APAC = Asia Pacific

Intent-to-Treat dataset: all subjects who received one dose of study medication and had one post-baseline assessment

- Statistically significant regional differences were found for every informant variable (all variables, $p < .001$).
- Parents were more frequently named as informant in Latin America (68%) and Europe (60%) than in North America/Asia Pacific (31%).
- Nearly a quarter (24%) of the informants in North America/Asia Pacific were acquaintances (e.g. friends, neighbors, other patients in residential facilities) compared to 6% and 4% in Europe and Latin America, respectively.
- Although medical/healthcare professionals were not often named as informants overall (10%), this was more common in North America/Asia Pacific (14%) than in Latin America (3%) and Europe (7%).
- Subjects in Europe and Latin America spent approximately 12 hours per week more on average with their informant than subjects in North America/Asia Pacific.
- Most subjects in Europe (72%) and Latin America (86%) lived with the named informant (interacting with subject daily and overnight), but this level of contact frequency was less common in North America/Asia Pacific (53%).

Quality Indicators

- Exploration of subject quality indicators in the overall program showed that the trial completion rate was 79.5%, PK-assessed drug compliance rate was 92%, and placebo non-response was 60% on the MCCB, 67% on the SCoRS, and 79% on the CGI-I. Trial quality indicators for the overall program and by region are outlined in Table 2.

Table 2. Quality indicator summary statistics, overall and by region

	NA/APAC (N=783)	EUR (N=550)	LATAM (N=154)	Overall (N=1487)	Overall (N=1487)
Trial completion, N (%)	566 (72.3)	477 (86.7)	140 (90.9)	1183 (79.5)	p < .001
Drug compliance, N (%)	471 (90.2)	343 (92.2)	101 (100)	915 (91.9)	p = .004
Placebo non-response, MCCB, N (%)	119 (66.1)	78 (52.0)	27 (61.4)	224 (60.0)	p = .032
Placebo non-response, SCoRS, N (%)	134 (65.7)	116(69.5)	33(67.35)	283 (67.3)	p = .743
Placebo non-response, CGI-I, N (%)	457 (78.8)	401 (82.5)	102(71.3)	960 (79.4)	p = .013

NA = North America, EUR = Europe, LATAM = Latin America, APAC = Asia Pacific

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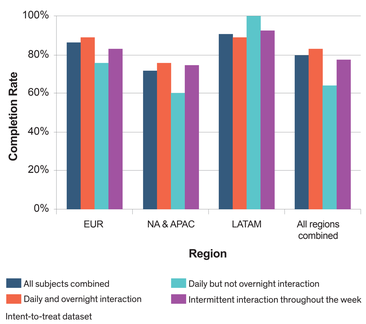
Informant characteristics as predictors of subject quality

- Informant variables as defined in Figure 1 were significantly related to one another (χ^2 range 232.95 to 1460.21, $p < .001$).
- Logistic regression showed that frequency of contact was the best predictor of subject quality, when quality is defined by trial completion ($\chi^2 = 20.01$, $p < 0.001$). No other informant characteristic significantly predicted completion rate, and none of the informant variables predicted PK compliance or placebo non-response.
- Of those subjects living with their informant (daily and overnight contact), 83% completed the trial, in contrast to 64% of subjects who had daily, but not overnight, contact with their informant (OR = 2.16, 95% CI: 1.47 to 3.17).
- To further explore why completion rates might be lowest in the group of subjects who had daily (but not overnight) contact with their informant, we examined the type of informant relationships most common in that group. Informants in this group were most frequently acquaintances (e.g. friends, neighbors, other patients in residential facilities; 35.4%), while in contrast, those informants with daily/overnight contact were most frequently parents (59.5%), and those with intermittent interaction throughout the week were most frequently medical/ healthcare professionals (32.3%).
- Independent variables region and contact frequency were significantly related to one another, suggesting that differences in informant contact frequency on completion rate could be explained by region, or in contrast, regional differences in completion rate could be explained by informant contact frequency.

Figure 2: Study Completion Rate by Region and Informant Contact Frequency



Intent-to-treat dataset

Influence of Informant Characteristics on MCCB-SCoRS Correlations

- The relationship between CIS cognitive performance measures and cognitive function has implications for scale validity and the ability to determine clinically meaningful change; though the strength of MCCB/SCoRS correlations may be impacted by factors such as availability and reliability of the informant (Keefe, 2015). For that reason, we examined whether characteristics of the subjects' informant, as defined in Figure 1, influenced the relationship between the MCCB and the SCoRS in the EVP 015/016 program.
- The overall correlation between SCoRS and MCCB at week 26 was -0.23 ($p = <.001$). MCCB-SCoRS correlations within each region were: -0.25 in North America/Asia Pacific, -0.24 in Europe, and -0.34 in Latin America.
- Correlations between MCCB and SCoRS were determined for every category of informant relationship, duration of relationship, and contact frequency, and are presented in Table 3. Correlations stronger than -0.20 were considered interpretable (Keefe et al., 2015).

Table 3: Relationships between MCCB and SCoRS by Informant Variable

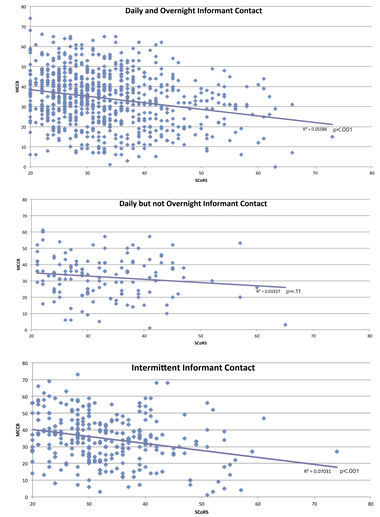
	Correlation between MCCB and SCoRS at Week 26		
Overall	**N**	**r**	**p**
	1179	-0.23	<.001
Contact Frequency			
Interacts with subject daily and overnight	770	-0.24	<.001
Interacts with subject daily, but not overnight	137	-0.14	0.11
Intermittent interaction throughout the week	270	-0.27	<.001
Informant Relationship			
Parent/custodian	557	-0.25	<.001
Significant other	160	-0.26	0.001
Child	36	-0.34	0.04
Sibling	84	-0.06	0.57
Extended family member	51	-0.11	0.45
Medical/healthcare professional	120	-0.39	<.001
Acquaintance	169	-0.16	0.04
Other	2	N/A	N/A
Duration of Relationship			
Lifetime	736	-0.22	<.001
5 years or more but less than lifetime	208	-0.23	0.001
1 year or more but less than 5 years	175	-0.30	<.001
8 weeks or more but less than 1 year	53	-0.18	0.19
Less than 8 weeks from screening	7	0.89	0.008

- Informant contact frequency, the variable identified as most predictive of trial completion, also influenced MCCB-SCoRS correlations. The correlation between MCCB and SCoRS for subjects with intermittent contact, as well as contact daily/overnight contact, were significant and comparable to the overall trial (daily/overnight: -0.24, $p < .001$; intermittent: $r = -0.27$, $p < .001$); however the MCCB-SCoRS correlation was not significant for subjects with daily informant contact ($r = -0.14$, $p = 0.11$).
- MCCB-SCoRS correlations were numerically stronger than the overall study sample for subjects whose informants were their children ($r = -0.34$, $p = 0.04$) or were medical/ healthcare professionals ($r = -0.39$, $p < .001$). The MCCB-SCoRS correlation for subjects who had known their informant between 1 and 5 years was -0.30 ($p < .001$). Interestingly, for subjects identifying an informant whom they had known for less than 8 weeks at study start, the MCCB-SCoRS correlation was strong and significant, but in the unexpected direction (i.e., one showing improvement while the other worsened; $r = 0.89$, $p < .01$).

Conclusions

- Exploration of subject informant characteristics in the EVP 6124 015/016 program unconvered significant regional differences on all informant variables: relationship to subject, duration of relationship, frequency of contact with subject, hours per week spent with subject (all $p < .001$).
- Parents were more frequently named as informant in Latin America (68%) and Europe (60%) than in North America/Asia Pacific (31%). Nearly a quarter (24%) of the informants in North America/Asia Pacific were acquaintances (e.g. friends, neighbors, other patients in residential facilities) compared to 6% and 4% in EU and Latin America, respectively.
- The markers defined for this analysis showed good overall trial quality, consistent with if not better than existing literature (e.g., Kahn, 2007; McCann 2015). Trial completion rate was 79.5%, PK-assessed drug compliance rate was 92%, and placebo non-response was 60% on the MCCB, 67% on the SCoRS, and 79% on the CGI-I.
- Analysis of informant characteristics showed that frequency of contact, but not type or duration of relationship, or weekly hours of interaction, was a significant predictor of subject quality (as defined by trial completion).
- Correlations between MCCB and SCoRS at week 26 were consistent with recent literature (Keefe, 2015), and the strength of the correlations were in part dependent on informant characteristics such as relationship and frequency of contact.
- Drug/placebo differences on the MCCB were greater in the 2 mg encenicline group than in the placebo group for those subjects who lived with their informants.
- These data may serve as a source for appropriate and operationally feasible definitions of informant reliability in future CIS protocols

Figure 3. MCCB-SCoRS Relationship, by Frequency of Informant Contact

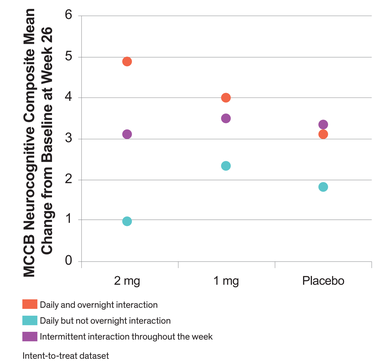


Intent-to-treat dataset

Impact of informant contact frequency on primary trial analysis

- Having identified informant contact frequency as a predictor of one pre-defined subject quality indicator, trial completion, we re-ran the original EVP-6124 015/016 primary analysis adding contact frequency into the MMRM model to determine whether this informant variable would influence the primary outcome. Results showed an important interaction between treatment group and informant contact frequency on the MCCB change from baseline score ($F(4,1304) = 2.08$, $p = 0.08$). In the 2 mg group, but not in the placebo or 1 mg groups, subjects living with their informant (i.e., daily and overnight contact) were more improved at endpoint than subjects with daily contact.

Figure 4: MCCB Change from Baseline by Dose Group and Informant Contact Frequency



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