

# Perspective on methodological challenges: How Phase 2 studies influence design & conduct of Phase 3

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# Overview

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## Objective:

- Describe elements of Phase 2B clinical trial that were considered and influenced the design of a Phase 3 Program

## Outline:

- Overview of Phase 2B study
- Key elements of study design and analyses
  - Measures of cognition: CogState OCI and MCCB
  - Functional Assessment
  - Subject subgroup analyses
- Key design elements of P3 study

**319 randomized patients (US and Russia, Ukraine, Serbia)**

**Subjects:** Schizophrenic patients in non-acute phase and on stable dose of atypical antipsychotic drugs

**Doses:** 0.3 mg, 1 mg, placebo

**QD for 12 weeks**

**Primary endpoint: Overall Cognition Index by CogState**

**Secondary endpoints**

- **MCCB** - MATRICS Consensus Cognitive Battery of tests (U.S.)
- **SCoRS** - Schizophrenia Cognition Rating Scale (cognition-based patient function)
- **PANSS** - Positive and Negative Syndrome Scale Score

# EVP-6124-009: Demographics

	Encenicline 0.3 mg N = 107	Encenicline 1 mg N = 105	Placebo N = 105	Total N = 317	p-value
<b>Gender, n(%)</b>					0.616
Male	70 (65.4)	75 (71.4)	70 (66.7)	215 (67.8)	
Female	37 (34.6)	30 (28.6)	35 (33.3)	102 (32.2)	
<b>Race, n (%)</b>					0.414
White	72 (67.3)	64 (61.0)	72 (68.6)	208 (65.6)	
Black	32 (29.9)	37 (35.2)	31 (29.5)	100 (31.5)	
Asian	3 (2.8)	1 (1.0)	2 (1.9)	6 (1.9)	
<b>Ethnicity, n (%)</b>					0.872
Hispanic	8 (7.5)	9 (8.6)	7 (6.7)	24 (7.6)	
Not Hispanic	99 (92.5)	96 (91.4)	98 (93.3)	293 (92.4)	
<b>Age (years)</b>					
18-30	27 (25.2)	33 (31.4)	26 (24.8)	86 (27.1)	
>30	80 (74.8)	72 (68.6)	79 (75.2)	231 (72.9)	
<b>Age (years)</b>					0.287
n	107	105	105	317	
Mean ± SD	39.1 ± 9.71	37.3 ± 10.51	39.2 ± 9.94	38.5 ± 10.07	
Median	39.0	36.0	40.0	38.0	
Range	21 - 55	18 - 55	20 - 54	18 - 55	

# EVP-6124-009: Demographics (Cont.)

	<b>Encenicline 0.3 mg N = 107</b>	<b>Encenicline 1 mg N = 105</b>	<b>Placebo N = 105</b>	<b>Total N = 317</b>	<b>p-value</b>
<b>BMI (kg/m<sup>2</sup> at screening)</b>					0.198
n	107	105	104	316	
Mean ± SD	27.00 ± 4.196	27.69 ± 4.30	28.05 ± 4.44	27.58 ± 4.31	
Median	26.44	28.10	28.94	27.64	
Range	18.3 – 35.0	16.5 – 34.8	18.6 – 35.0	16.5 – 35.0	
<b>Years since disease onset, n (%)</b>					0.136
< 10 years	44 (41.1)	55 (52.4)	42 (40.0)	141 (44.5)	
≥ 10 years	63 (58.9)	50 (47.6)	63 (60.0)	176 (55.5)	
<b>Continent, n (%)</b>					0.914
US	57 (53.3)	55 (52.4)	58 (55.2)	170 (53.6)	
Europe	50 (46.7)	50 (47.6)	47 (44.8)	147 (46.4)	
<b>Antipsychotic, n (%)</b>					0.314
Risperidone	51 (47.7)	53 (50.5)	52 (49.5)	156 (49.2)	
Olanzapine	17 (15.9)	7 (6.7)	11 (10.5)	35 (11.0)	
Other	39 (36.4)	45 (42.9)	42 (40.0)	126 (39.7)	

## EVP-6124-009: Subject disposition

Status	Encenicline 0.3 mg n (%)	Encenicline 1 mg n (%)	Placebo n (%)	Total n (%)
Screened				442
Randomized	107	106	106	319
Completed day 28	100 (93.5)	102 (96.2)	98 (92.5)	300 (94.0)
Completed study	93 (86.9)	88 (83.0)	84 (79.2)	265 (83.1)
Discontinued early	14 (13.1)	18 (17.0)	22 (20.8)	54 (16.9)

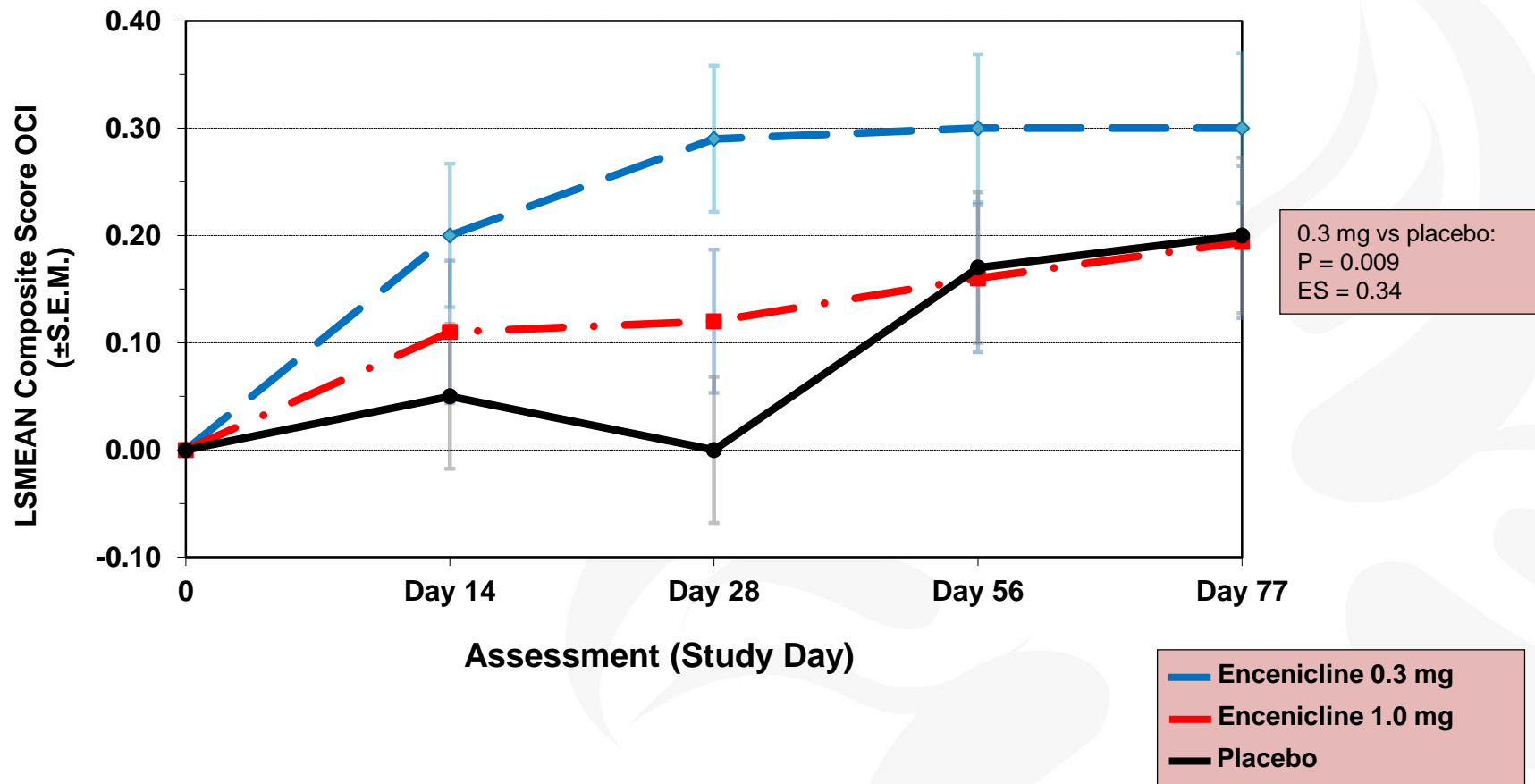
# EVP-6124-009: Overall Summary of AEs

	<b>Encenicline 0.3 mg N = 107 n (%)</b>	<b>Encenicline 1 mg N = 105 n (%)</b>	<b>Placebo N = 105 n (%)</b>	<b>Total N = 317 n (%)</b>
<b>Subjects with any TEAE</b>	25 (23.4)	35 (33.3)	41 (39.0)	101 (31.9)
<b>Total number of TEAEs</b>	43	60	89	192
<b>Subjects with any treatment-related AE</b>	8 (7.5)	16 (15.2)	11 (10.5)	35 (11.0)
<b>Total Treatment-related AEs</b>	11	21	21	53
<b>Subjects with any SAE</b>	1 (0.9)	3 (2.9)	2 (1.9)	6 (1.9)
<b>Total SAEs</b>	1	3	2	6
<b>Subjects with any related SAE</b>	0	0	0	0
<b>Total Related SAEs</b>	0	0	0	0
<b>Subjects with AE leading to drug discontinuation</b>	2 (1.9)	5 (4.8)	9 (8.6)	16 (5.0)
<b>Total AEs leading to drug discontinuation</b>	2	7	13	22
<b>Subjects with any AE leading to death</b>	0	0	0	0
<b>Total AEs leading to death</b>	0	0	0	0
AE = Adverse event      TEAE = Treatment emergent adverse event      SAE = Serious adverse event				

# EVP-6124-009: Adverse Events (> 2%)

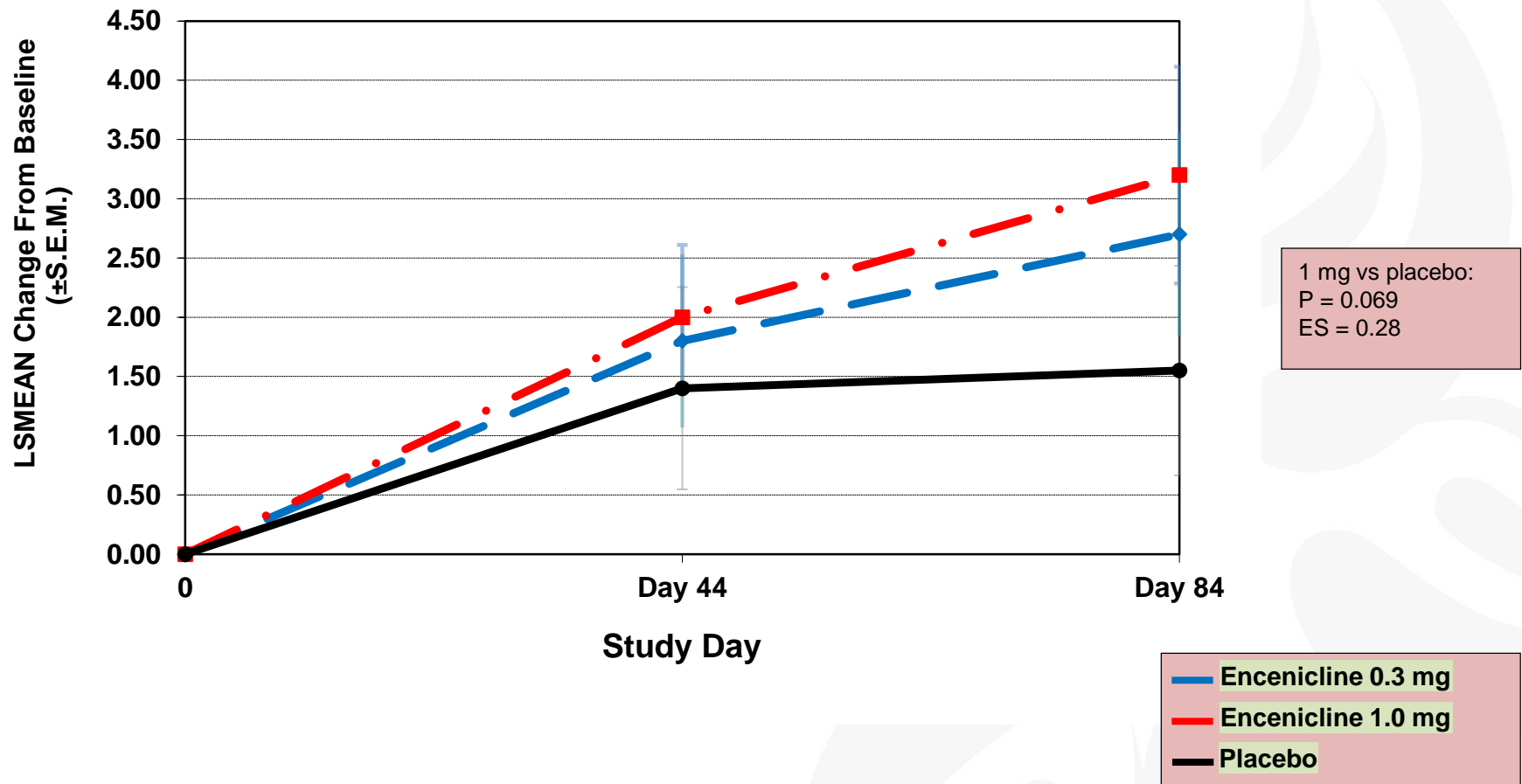
	<b>Encenicline 0.3 mg N = 107</b>	<b>Encenicline 1 mg N = 105</b>	<b>Placebo N = 105</b>	<b>Total N = 317</b>
<b>System Organ Class / preferred term</b>	Subjects n (%) / n AE	Subjects n (%) / n AE	Subjects n (%) / n AE	Subjects n (%) / n AE
<b>Overall</b>	25 (23.4) / 43	35 (33.3) / 60	41 (39.0) / 89	101 (31.9) / 192
<b>Gastrointestinal</b>	5 (4.7) / 5	10 (9.5) / 14	6 (5.7) / 8	21 (6.6) / 27
Nausea	1 (0.9) / 1	4 (3.8) / 4	5 (4.8) / 5	10 (3.2) / 10
<b>General admin and site</b>	2 (1.9) / 2	4 (3.8) / 5	8 (7.6) / 9	14 (4.4) / 16
Pyrexia	0 / 0	0 / 0	4 (3.8) / 4	4 (1.3) / 4
<b>Infections and infestations</b>	8 (7.5) / 9	9 (8.6) / 10	13 (12.4) / 13	30 (9.5) / 32
Nasopharyngitis	2 (1.9) / 2	4 (3.8) / 4	2 (1.9) / 2	8 (2.5) / 8
<b>Investigations</b>	3 (2.8) / 3	3 (2.9) / 3	9 (8.6) / 14	15 (4.7) / 20
CPK increased	1 (0.9) / 1	0 / 0	4 (3.8) / 4	5 (1.6) / 5
<b>Musculoskeletal and connective tissue</b>	1 (0.9) / 2	1 (1.0) / 1	4 (3.8) / 4	6 (1.9) / 7
Back pain	0 / 0	0 / 0	3 (2.9) / 3	3 (0.9) / 3
<b>Nervous system disorders</b>	7 (6.5) / 8	12 (11.4) / 12	7 (6.7) / 7	26 (8.2) / 27
Headache	5 (4.7) / 6	5 (4.8) / 5	2 (1.9) / 2	12 (3.8) / 13
Dizziness	1 (0.9) / 1	3 (2.9) / 3	1 (1.0) / 1	5 (1.6) / 5
<b>Psychiatric disorders</b>	5 (4.7) / 8	3 (2.9) / 3	6 (5.7) / 10	14 (4.4) / 21
Anxiety	3 (2.8) / 3	0 / 0	2 (1.9) / 2	5 (1.6) / 5
<b>Skin and subcutaneous tissue</b>	0 / 0	4 (3.8) / 5	1 (1.0) / 1	5 (1.6) / 6
Rash	0 / 0	3 (2.9) / 4	0 / 0	3 (0.9) / 4

# Study EVP-6124-009: Cognition (CogState Battery OCI)



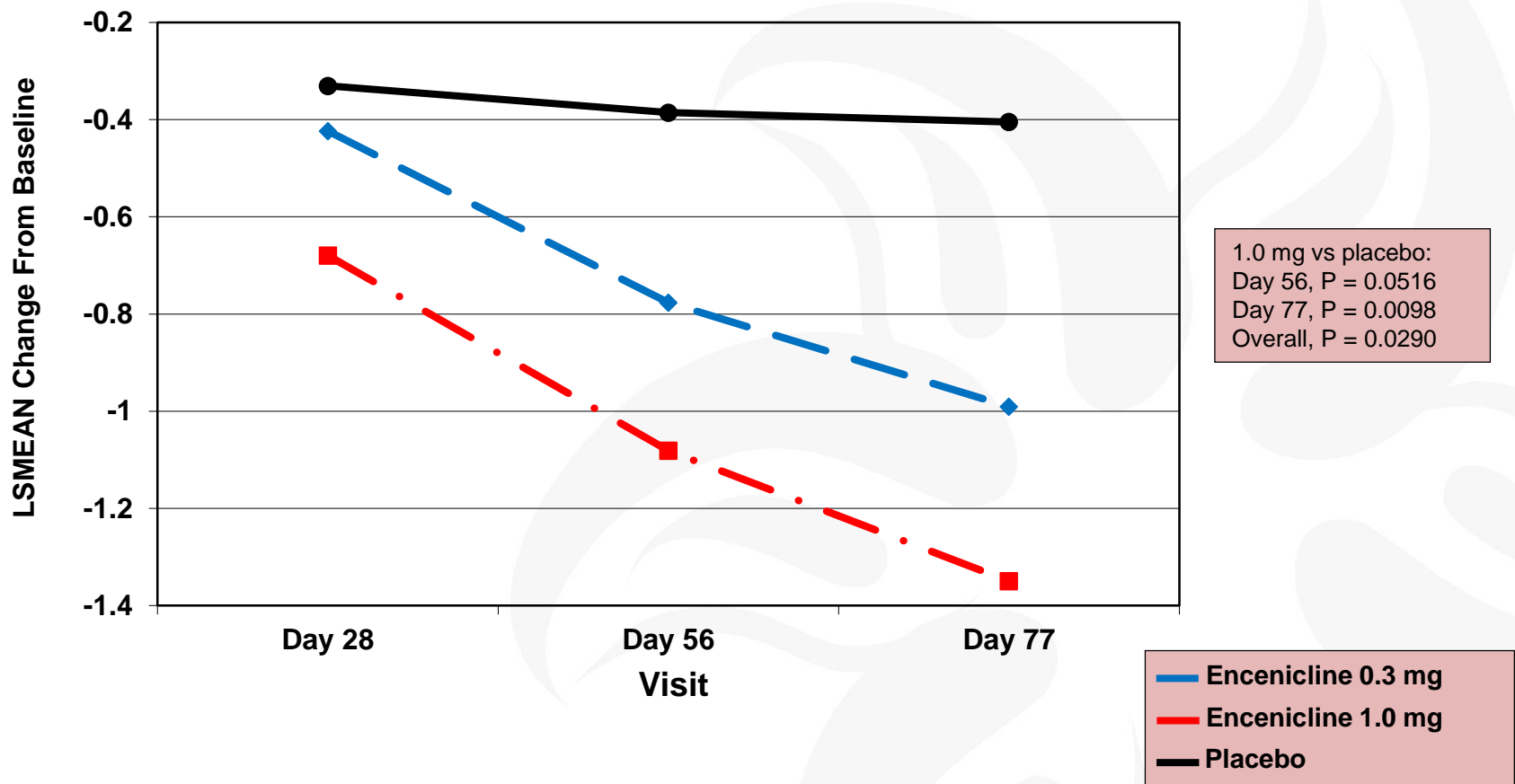
# Cognition (MCCB) in US Subjects

**MCCB (LOCF)  
(Adjusted Mean Change from Baseline)**



# EVP-6124-009 PANSS Subscore Domains<sup>1</sup>

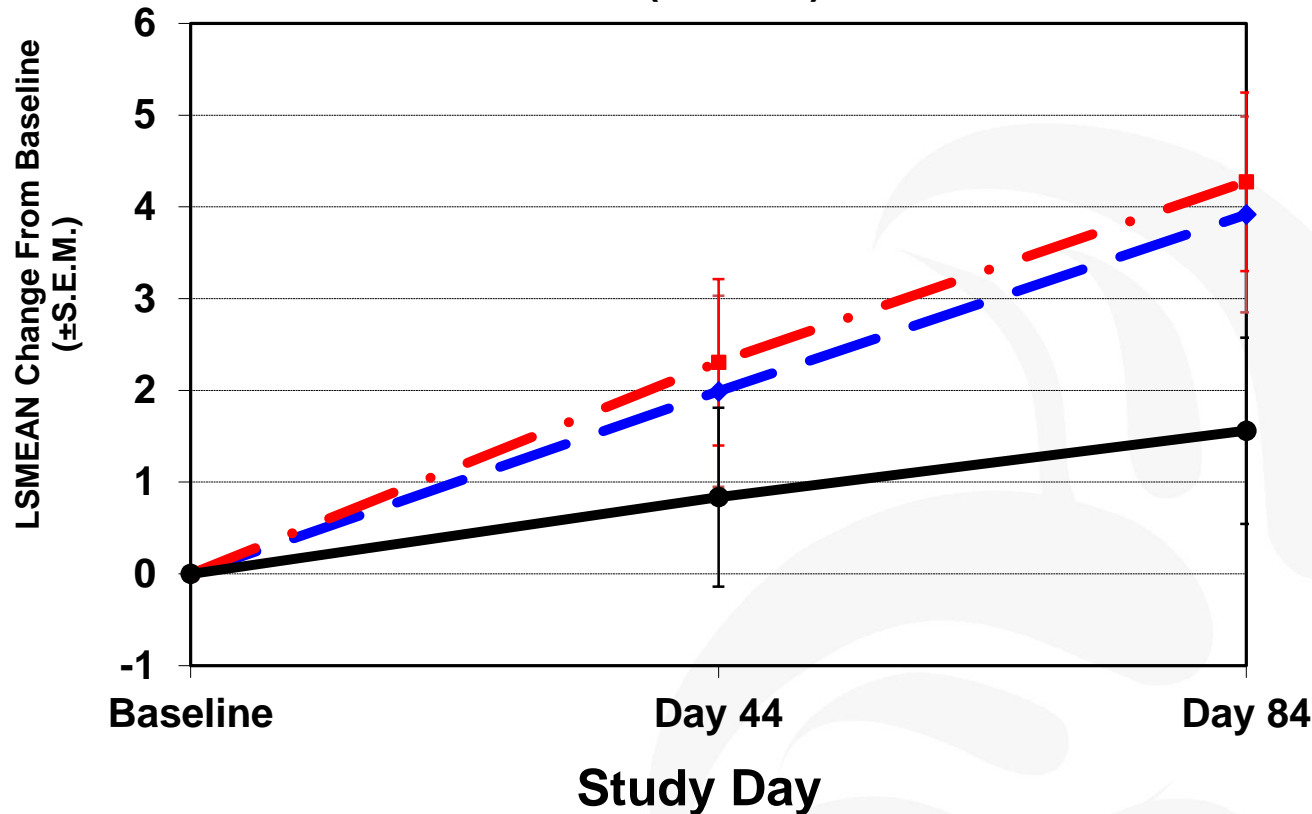
## PANSS “Cognitive Impairment” Domain<sup>1</sup> (Decrease indicates improvement)



<sup>1</sup>Domains based on: Mohr PE, et al. The heterogeneity of schizophrenia in disease states. *Schizophr Res.* 2004;(71):83-85.

# EVP-6124-009: MCCB (US Patients Only)

Aged  $\leq 50$  years  
(N = 108)

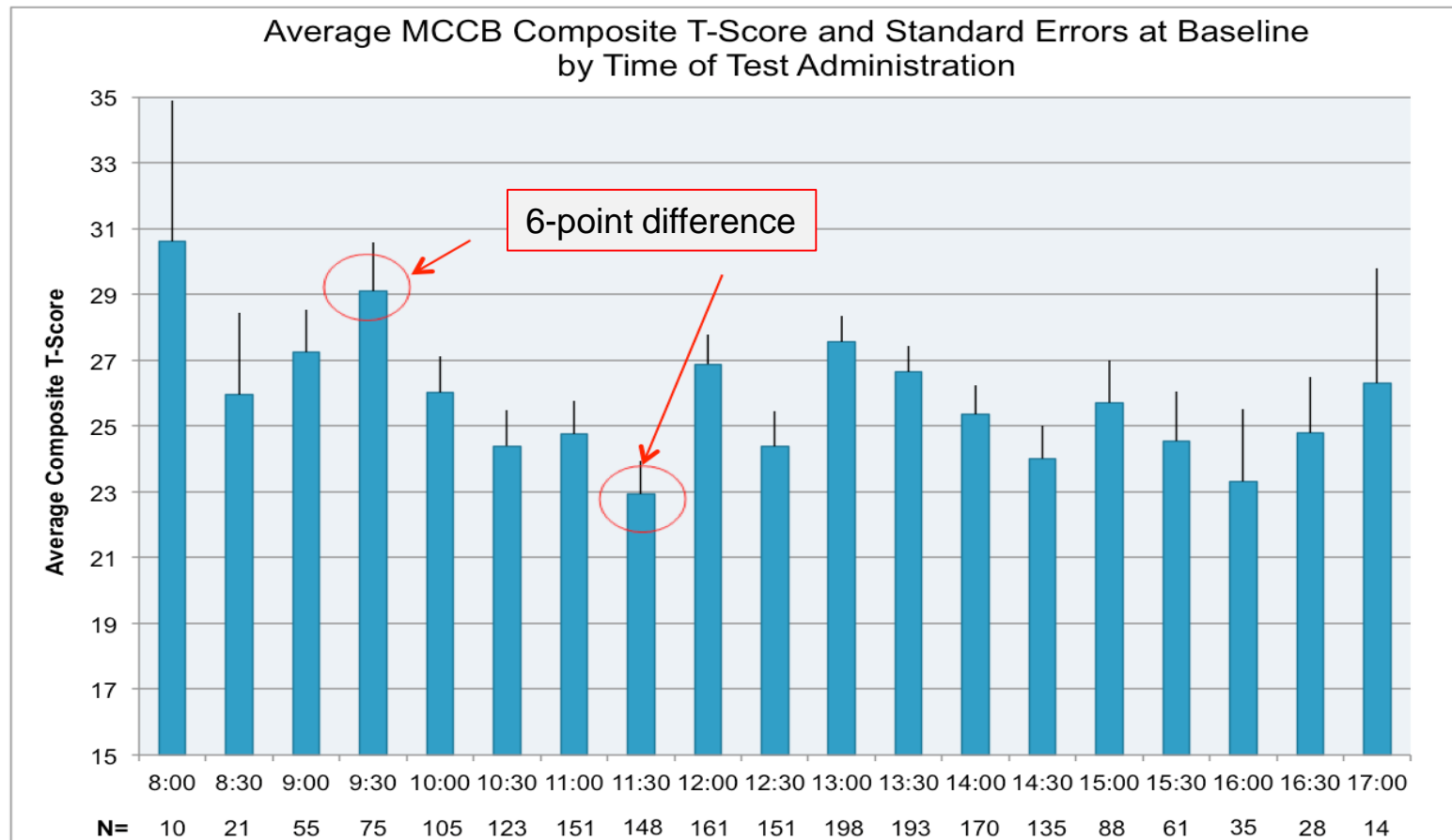


**Encenicline (EVP-6124)**  
**1 mg vs placebo**  
Day 84:  $P = 0.058$  ES = 0.48  
Overall:  $P = 0.083$  ES = 0.40

**Encenicline (EVP-6124)**  
**0.3 mg vs placebo**  
Day 84:  $P = 0.114$  ES = 0.41  
Overall:  $P = 0.169$  ES = 0.34

—◆— Encenicline 0.3 mg  
—□— Encenicline 1.0 mg  
—○— Placebo

# MCCB score shows some fluctuation across time of day



# MCCB Summary and Conclusions based on P2 Study

## **Conclusions based on FRM P2 study**

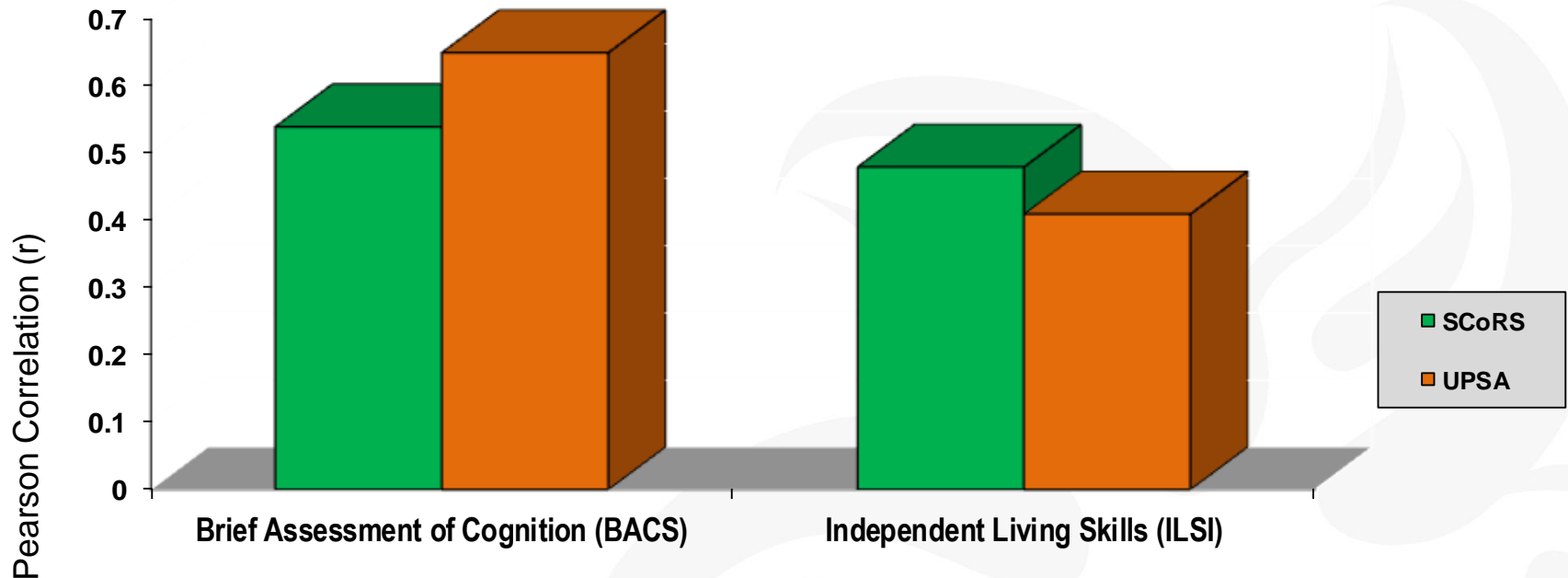
- MCCB provided ability to detect signal consistent with the PANSS Cognitive Subscore and functional endpoint (SCoRS)
- Practice effect seen -- may be more prominent between first and second administration; administration prior to randomization should be considered
- Time of day may add to variability of MCCB
  - Along with subject fatigue; sobriety
- Ability to detect signal may be enhanced in subjects < 50 year old

# Schizophrenia Cognition Rating Scale (SCoRS)

- 20 anchored items rated 1 (none) to 4 (severe)
- Assesses all 7 MATRICS cognitive domains
  - Memory: 4 items
  - Learning: 2 items
  - Attention: 3 items
  - Working memory: 2 items
  - Problem solving: 3 items
  - Processing/motor speed: 2 items
  - Social cognition: 3 items
  - Language: 1 item
- Format:
  - Patient and informant interview
  - Global/Interview Score determined by interviewer at each visit
  - Follow-up ratings include Global Change measure
- Time:
  - ≤ 20 minutes per interview (for both subject and informant)
- Psychometrics:
  - Inter-rater reliability on 11 patients was very high (ICC > 0.90 for all but one item, which was eliminated)
  - PASS test-retest reliability
    - patient only rating: ICC=0.60
    - interviewer rating: ICC=0.82

# SCoRS shows good correlation with measures of cognitive performance

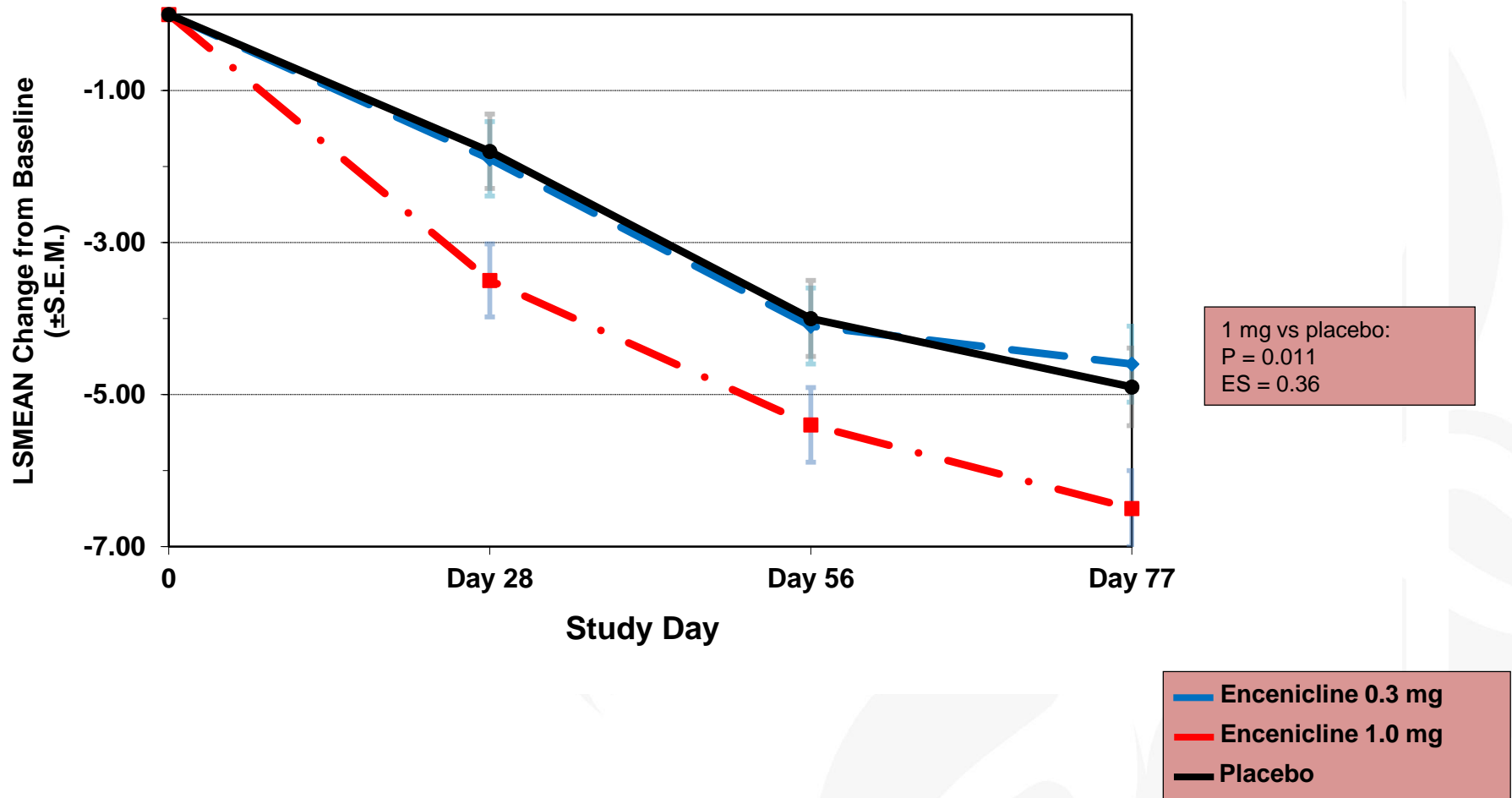
Correlation of SCoRS and UPSA:  $r = 0.53$



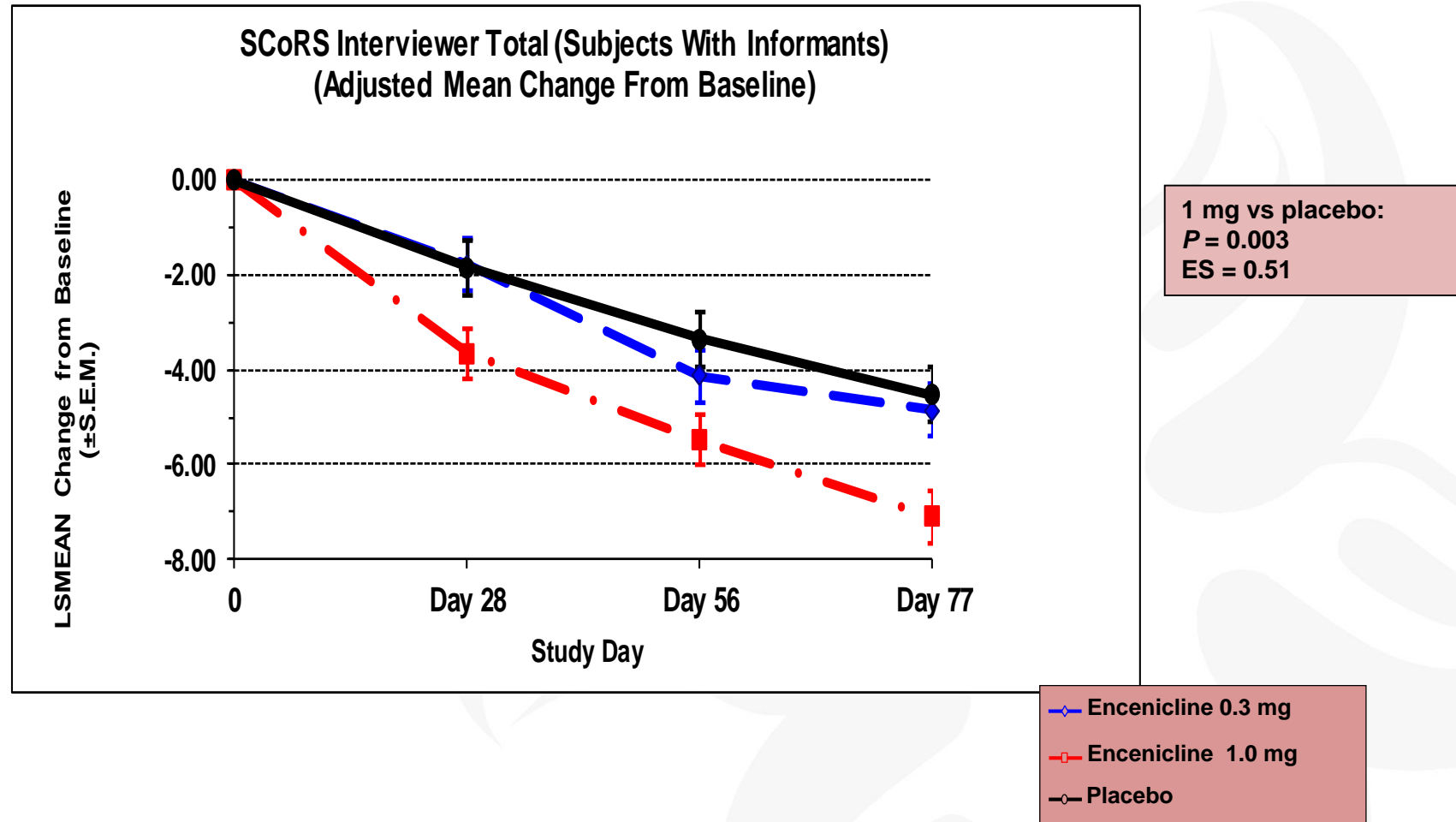
Correlations of SCoRS and UPSA with Cognitive Performance (BACS) and Functional Outcome ILSI) in Schizophrenia (N=60)

## EVP-6124-009 SCoRS (Function)

SCoRS Interviewer Total  
(Adjusted Mean Change From Baseline)

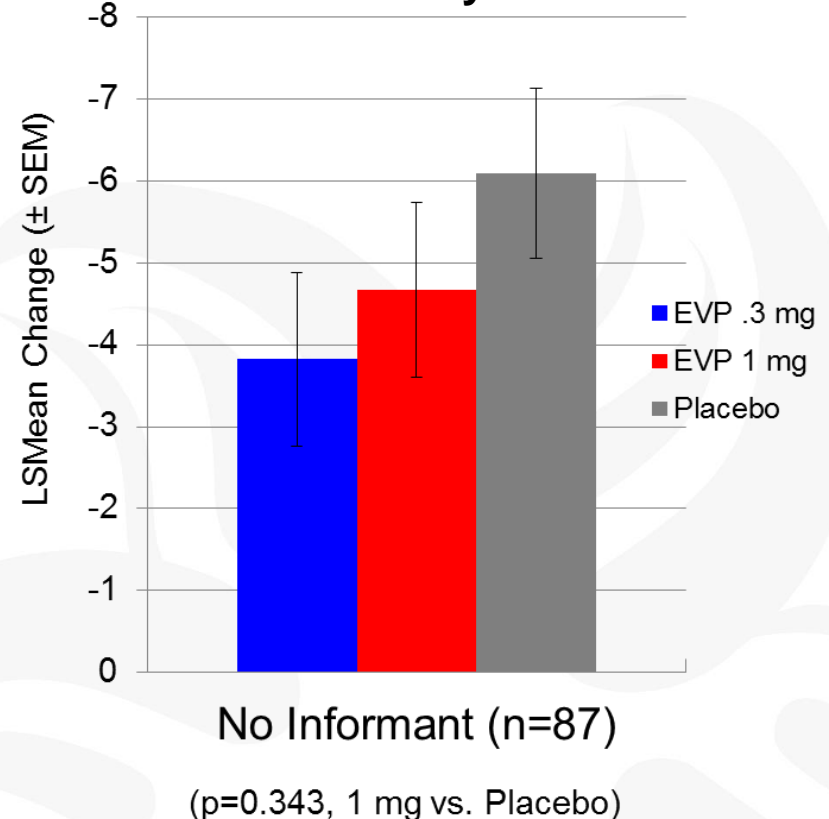
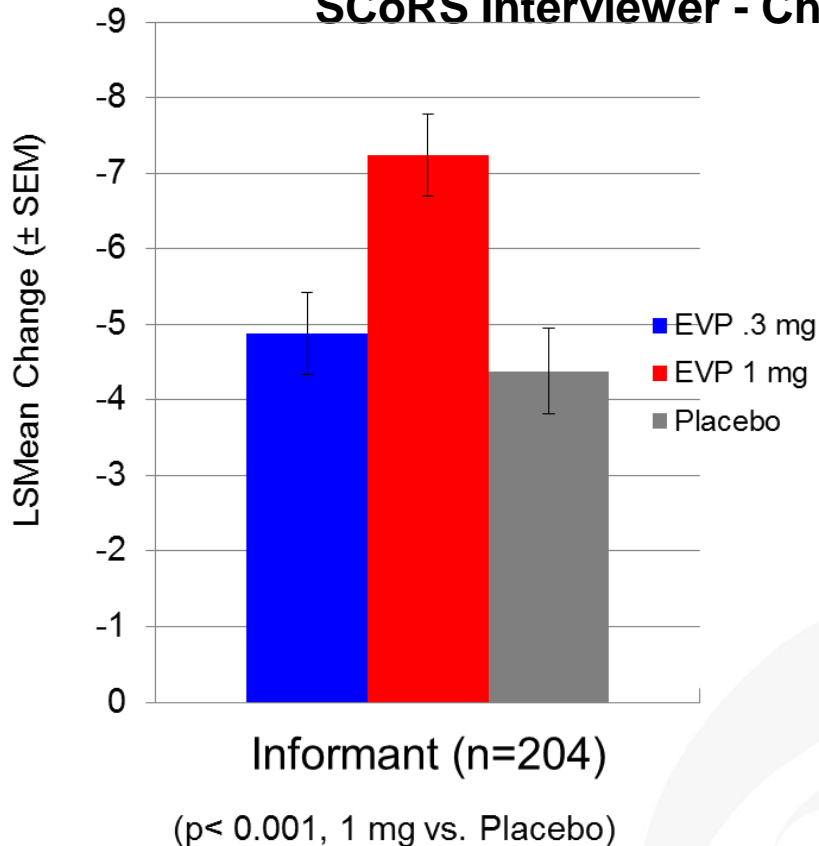


# SCoRS (Visits With Informant Present)



# Subgroup Analysis of subjects with and without Informant

## SCoRS Interviewer - Change from Baseline to Day 77



### Conclusions based on FRM P2 study

- SCoRs is a valid and reliable measure which showed ability to detect signal in P2b Study
- Ability to detect signal may be enhanced in the subset of subjects with informants

# Post-hoc Subgroup Analyses of Phase 2b Study

<b>Endpoint</b>	<b>Factor</b>	<b>Covariate p-value</b>	<b>Interaction p-value (trt x factor)</b>
<b>MCCB</b> (Composite T-score)	<b>Smokers vs. Non-Smokers</b>	<b>0.752</b>	<b>0.976</b>
<b>MCCB</b>	<b>Males vs. Females</b>	<b>0.952</b>	<b>0.453</b>
<b>MCCB</b>	<b>Schizophrenia vs. Schizo-affective Disorder</b>	<b>0.101</b>	<b>0.552</b>
<b>MCCB</b>	<b>Baseline PANSS total severity</b>	<b>0.166</b>	<b>0.711</b>
<b>MCCB</b>	<b>Baseline PANSS negative subscale severity</b>	<b>0.229</b>	<b>0.762</b>
<b>MCCB</b>	<b>Baseline PANSS positive subscale severity</b>	<b>0.186</b>	<b>0.754</b>

## Conclusions based on FRM P2 study

- Generalizability of study population is an important consideration in study design
- In the absence of clear signal, aligned with regulatory input, minimal restrictions to patient population were recommended in FRM P3 program

# Additional Post-hoc Analyses – Phase 2b

## MCCB and Exclusion of MSCEIT

	Change from Baseline Over All Visits			
		EVP 0.3 mg	EVP 1 mg	Placebo
<b>MCCB Composite T-score, Including All Domains</b>	N LSMean SEM	47 2.6 0.74	48 2.8 0.75	45 1.8 0.77
<b>MCCB, Excluding MSCEIT</b>	N LSMean SEM	47 1.9 0.48	48 2.1 0.48	45 1.1 0.50
<b>MCCB, Excluding MSCEIT; Restricted to Subjects ≤ 50 Years Old</b>	N LSMean SEM	31 2.2 0.59 (0.3 mg vs. placebo, p=0.055)	41 2.4 0.52 (1 mg vs. placebo, p=0.024)	36 0.6 0.56

# Encenicline Phase 3 Trial Design

**700 randomized patients per trial (US and 15 OUS countries)**

**Subjects:** Schizophrenic patients in non-acute phase and on stable dose of atypical antipsychotic drugs

**Doses:** 1 mg, 2 mg, and placebo

**QD for 26 weeks (with 26-week safety extension)**

**Co-primary endpoints:** MCCB Composite T-score – (MATRICS Consensus Cognitive Battery) of tests, and SCoRS (Schizophrenia Rating Cognition Scale) Interviewer total score

**Secondary endpoints**

- **MCCB** – cognition composite excluding MSCEIT
- **PANSS**
- **CGI-S** and **CGI-C**
- **EQ-5D** – EuroQoL-5D

# Site and subject burden are substantial in a P3 Program

- Overall time required for assessments is vastly different from other psychiatric trials
  - Regulatory requirements and other considerations may cause even further burden on P3 programs over and above P2 studies
    - Subject burden and fatigue/ability to engage should be considered
      - Prepare sites and subjects
    - Site experience and resources for burdensome studies
  - Learnings from completed P3 program will provide further operational insights
- 
- Careful rater training and continued remediation likely to be important
    - Will need to be balanced with overall study burden

# Summary of Key Differences between Encenicline Phase 2b Study and Phase 3 Studies

<i><b>Phase 2b</b></i>	<i><b>Phase 3</b></i>
Doses 0.3mg, 1mg, PBO	1mg, 2mg, PBO
3m double-blind observation period	6m double-blind observation period
Primary endpoint OCI Cog State	Primary endpoints: MCCB, SCoRS
Age range 18-55	Age range 18-50
Informant requested	Informant required
Single atypical antipsychotic	Up to 2 atypical antipsychotic allowed
Diagnosis of schizophrenia or schizo-affective disorder	Diagnosis of schizophrenia

# Phase 3 Program substantially more complex than Phase 2B

## **Site and subject burden are substantial**

- Overall time required for assessments is notably different from other psychiatric trials
- Regulatory requirements and other considerations may contribute to further complexity of P3 programs over and above P2 studies
- Subject burden and fatigue/ability to engage should be considered
  - Prepare sites and subjects

## **Global experience limited**

- Rating scales – MCCB validated versions; SCoRS
- Use of informants/caregivers
- Overall burden of study
- Careful rater training and continued remediation likely to be important
  - Will need to be balanced with overall study burden

## **Longterm care of patients with schizophrenia vary across regions/countries – challenges for adjunctive treatment study**

- Living situation – long-term hospitalization vs facilitated living vs home care
- Antipsychotic medication



**Learnings from completed P3 program will provide further operational insights**