**METHODS**

- **Schizophrenic subjects** (n=319) stably treated with second generation atypical antipsychotic drugs
- **Parallel, double-blind design**: placebo, 0.3, 1.0 mg/day for 12 weeks
- **Trial conducted in the US and Eastern Europe** (Ukraine, Serbia, Russia)
- **Efficacy Measures**:  
  - **Primary Endpoint**  
    - Overall Cognition Index by CogState (OCI-Computerized cognitive measurement)
  - **Secondary endpoints**:  
    - MCCB Battery – MATRICS Consensus Cognitive Battery
    - SCoRS – Clinical rating of patient function based on cognition (Keefe et al., 2006)
    - PANSS – Positive and Negative Syndrome Score (Overall PANSS, Positive Symptom Score, Negative Symptom Score)
  - **MCCB data** captured among patients at the U.S. sites (N=140)

**RESULTS**

- **Spider Plot Overview**
- **MCCB Score Changes**  
  - MCCB Subtest Changes at Day 84 (ITT population)

**Figure 1**: Temporal Patterning of Change Over Time

**Figure 2,3**: Impact of an Informant on Schizophrenia Cognition Rating Scale Data

**CONCLUSIONS**

- The temporal patterning of cognitive changes over time – with the vast majority of improvement in the placebo group manifesting itself by Day 44 – confirms the importance of trial duration as one key factor in helping to distinguish between practice effects and placebo versus pharmacodynamic-induced changes
- When capturing subjective impressions of cognitive functioning, the presence of an informant may help to enhance signal detection as compared to relying solely on patient self-reports

**REFERENCES**

- Mallinckrodt CH. Tamura, RN, Tanaka, Y: Recent developments in improving signal detection in clinical trials of novel pharmacotherapies for schizophrenia (Mallinckrodt et al., 2011)
- We examined two methodological issues affecting signal detection in a clinical trial of EVP-6124, a selective, potent, oral nicotinic alpha-7 agonist being developed for cognitive impairments in schizophrenia

**SAFETY & EFFICACY**

- EVP-6124 was safe, well tolerated and had clinically meaningful effects compared to placebo on cognitive performance (CogState and MATRICS Consensus Cognitive Battery [MCCB-in US subjects only]) and interview-based assessments (Schizophrenia Cognition Rating Scale [SCoRS]) as well as negative symptoms
  - For more information, see:
- Clinicaltrials.gov identifier: NCT00968851

**Temporal Patterning of MCCB Response**

- We explored the temporal patterning of responses on the MCCB by examining what percentage of total change had occurred at the Day 44 vs. the Day 84 visit
- Placebo patients manifested 94% of their total change by the Day 44 visit, compared to only 61% and 56% for the 0.3 and 1.0 mg EVP-6124 groups, respectively (see Figure 1)
- In short, nearly all of the placebo effect’s total impact on the MCCB was detected by Day 44, whereas both EVP-6124 groups continued to show substantial cognitive improvements in the latter half of the trial

**Impact of an Informant on SCoRS Data**

- We also examined whether the presence of an informant would help to provide a more sensitive test of cognitive improvements on the SCoRS
- Consistent with previous research, we found that the presence of an informant helped to increase the effect sizes (ES) (1.0 mg EVP-6124 subjects vs. placebo with no informant: ES=.36; with an informant: ES=.51) (see Figures 2 & 3)

**AUTHOR DISCLOSURES**

- Michael R Hufford, Maria Gawryl, Nancy Dgetluck, Vicki G Davis, Stephen Murray, Richard SE Keefe, Dana Hilt
- 1 NeuroCog Trials, Inc. (Durham, NC), 2 EnVivo Pharmaceuticals (Watertown, MA), 3 Duke University (Durham, NC)

* Data from the MCCB was only captured from patients in the United States. Data from 14 early termination visits conducted outside the scheduled visit window were excluded from this analysis.

**METHODS**

- A variety of methodological issues can significantly impact signal detection in clinical trials of novel pharmacotherapies for schizophrenia (Mallinckrodt et al., 2011)
- We examined two methodological issues affecting signal detection in a clinical trial of EVP-6124, a selective, potent, oral nicotinic alpha-7 agonist being developed for cognitive impairments in schizophrenia