



EVP-6124 - Safety, Tolerability and Cognitive Effects of a Novel $\alpha 7$ Nicotinic Receptor Agonist in Alzheimer's Disease Patients on Stable Donepezil or Rivastigmine Therapy

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ABSTRACT

Approved symptomatic therapies for Alzheimer's disease (AD) provide modest relief. In the future, it is likely that symptomatic treatments will be utilized with AD modifying therapies, the development of which are currently a primary focus of research. The nicotinic $\alpha 7$ receptor agonist may be an attractive drug candidate to potentially improve cognition in Alzheimer's disease patients either as a stand-alone therapy or in combination with other symptomatic treatments.

EVP-6124 is a novel, potent, and selective $\alpha 7$ nicotinic receptor agonist. EVP-6124 has an excellent brain to plasma exposure ratio and has shown excellent efficacy and potency in a number of animal models of cognition. Four clinical studies in >125 healthy normal human subjects have been completed with EVP-6124, including a single-ascending-dose study, a 14-day multiple-ascending-dose study, a 21-day, multiple-dose study, and a single-dose relative bioavailability, food and gender effect study. EVP-6124 exhibited linear kinetics over the range of 1 to 180 mg and demonstrated a half-life suitable for once daily dosing. EVP-6124 appears to be safe and well-tolerated for up to 21 days as measured by adverse events, vital signs, continuous cardiac monitoring, physical examination, and clinical laboratory evaluations. In addition, in normal volunteers, EVP-6124 demonstrated pro-cognitive effects (CogState testing) in various cognitive domains including executive function.

The safety and efficacy of EVP-6124 was assessed in a Phase 1b study of 48 mild to moderate AD patients 60-80 years of age, on stable donepezil or rivastigmine therapy. Patients were dosed with placebo or two different doses of EVP-6124 (0.3 or 1.0 mg/d) for 28 days. Safety was evaluated by adverse events, ECG, and clinical laboratory measures. Cognitive effects were measured by CogState computerized cognitive testing and a subset of NTB scales.

EVP-6124 appeared to be safe and well tolerated with no significant adverse events reported more frequently in treated versus placebo patients; there were no SAEs reported. Subjects exposed to EVP-6124 in addition to donepezil or rivastigmine showed an increase in cognitive function, primarily in the domains of non-verbal learning, memory, and executive function.

These data suggest that EVP-6124 administered to AD subjects on stable cholinesterase inhibitor therapies, may have potential benefit and that further study in this patient population is indicated. Larger phase II studies are currently being initiated in both Alzheimer's disease and schizophrenia.

INTRODUCTION

Nicotinic Alpha-7 Receptor: Validated Target for Cognition

- Multiple selective agonists (AR-R-17779, EVP-6124, SSR180711, MEM3454, A-582941) improve memory in animals
- Memory/s/Roche MEM3454 has shown promising phase IIa data in Alzheimer's patients
- Amyloid peptide Ab42 peptide interacts with $\alpha 7$ receptor subtypes in vitro
- Multiple data suggesting potential impact on disease progression

METHODS

- Randomised, double-blind, placebo-controlled, ascending dose in patients with mild to moderate probable Alzheimer's disease (AD)
- 3 days observation, 1 month active or placebo dosing (5 days under observation/in-patient and 23 days outpatient)
- 4 groups; 12 patients/group
- 0.1, 0.3, or 1.0 mg of EVP-6124, placebo
- AD patients stabilized on AChEI (donepezil or rivastigmine)

Primary endpoints

- Safety, clinical safety and laboratory assessments

Secondary endpoints

- PK of EVP-6124 and AChE Inhibitors for potential drug-drug interactions

Tertiary endpoints

- Cognition testing (CogState and subset of NTB scales)

Inclusion Criteria

- Male or female, 50-80 years old
- Probable AD consistent with NINCDS and ADLDA criteria
- MRI or computed tomography (CT) scan within 24 months
- MMSE score of 18-26 at screening
- Modified Hachinski Ischemic Score ≤ 4
- Patient living in setting not requiring continuous nursing care
- Patient on stable dose of AChEI (donepezil or rivastigmine) for at least 4 months prior to study initiation
- If prior treatment with either memantine or galantamine, neither medication within 28 days of baseline

Main Exclusion Criteria

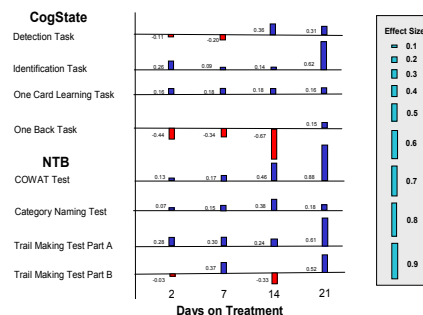
- Hospitalization within 4 weeks before or during screening period
- Participation in another clinical trial within 3 months
- Untreated hypothyroidism
- Insufficiently controlled diabetes mellitus
- Renal insufficiency
- Significant cardiovascular disease
- Major depression within the last five years
- Geriatric Depression Scale score > 5
- Stroke within six months before screening, or concomitant with onset of dementia
- Specific degenerative CNS disease diagnosis other than Alzheimer's disease (e.g., Huntington's disease, Jacob-Creutzfeldt disease, Down syndrome)

RESULTS

CogState/NTB Outcome Measures

CogState		NTB	
Task Name	Cognitive Domain	Task Name	Cognitive Domain
Detection	Psychomotor Function	Controlled Oral Word Association	Verbal Fluency
Identification	Visual Attention	Category Naming	Language
One Card Learning	Learning	Trail Making Part A	Attention, cognitive processing speed
One Back	Working Memory	Trail Making Part B	Visual searching, cognitive processing speed

Effect Size of 1 mg Dose In Pilot AD Study



Cognition Dose-Response Analysis

A number of cognition measurements demonstrated statistically significant dose dependent effects

- Detection task (p=0.01)
- Identification task (p=0.03)
- COWAT (p=0.04)
- CNT (p=0.02)
- Trails A (p=0.17)
- Trails B (p=0.13)

Adverse Events per Body System

	Placebo (N=12)	EVP-6124 0.1mg (N=12)	EVP-6124 0.3mg (N=12)	EVP-6124 1.0mg (N=12)	Total (N=48)
System Organ Class/preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	4 (33.3) / 6	2 (16.7) / 6	3 (25.0) / 4	4 (33.3) / 5	13 (26.5) / 23
Laboratory	0	0	0	1 (8.3) / 1	1 (2.1) / 1
Eye Disorders	1 (8.3) / 1	0	0	0	1 (2.1) / 1
Cardiovascular	0	0	0	2 (16.7) / 2	2 (4.2) / 2
Abuse	0	2 (16.7) / 2	0	0	2 (4.2) / 2
Alcohol	0	2 (16.7) / 2	0	0	2 (4.2) / 2
Infections & Infestations	0	0	0	1 (8.3) / 1	1 (2.1) / 1
Respiratory System	1 (8.3) / 2	2 (16.7) / 2	0	0	3 (6.3) / 4
Psychiatric Disorders	0	0	0	0	0
Neoplasms	0	0	1 (8.3) / 1	0	1 (2.1) / 1
Neurology	1 (8.3) / 1	0	0	0	1 (2.1) / 1
Skin Disorders	0	0	1 (8.3) / 1	0	1 (2.1) / 1
Investigations	1 (8.3) / 1	0	0	0	1 (2.1) / 1
Overall	0	0	1 (8.3) / 1	0	1 (2.1) / 1

EVP-6124 SUMMARY

- EVP-6124 safe and well tolerated (up to 28 days) in AD patients on long-term AChEI therapy
- Pro-cognitive effects in addition to AChEI were observed
 - Effects appear to increase over the treatment period
 - Effects are dose dependent for several cognition measurements
- EVP-6124 has normalizing effects on a number of evoked response biomarkers in schizophrenic patients on long term atypical, antipsychotic therapy (presented at upcoming ACNP meeting)

HYPOTHESIS

- EVP-6124 may have pro-cognitive and clinical benefits when added to long term AChEI therapy in mild/moderate AD patients
- Warrants further studies to define the magnitude of pro-cognitive effects and potential clinical benefits in both AD and schizophrenia