A PRE-Pivotal Study: β-Amyloid Plaque Detection in the LENS of the Eye in MCI and Mild AD - Correlation with Amyloid PET Scanning

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INTRODUCTION

20 years or more before symptoms appear, the brain changes of Alzheimer's begin [1-4].

Numerous studies have shown that cognitively unimpaired individuals or patients with MCI with abnormal amyloid biomarkers have more rapid progression of atrophy, hypometabolism or clinical/cognitive decline than individuals without biomarker evidence of β-amyloid deposition. [5-8]

The first biomarkers to become abnormal in carriers of deterministic AD mutations are those of β-amyloid [5,6]

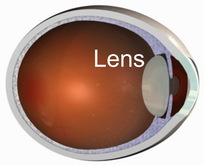
There is a profound need for a diagnostic to rapidly and easily identify b-amyloid deposition as a means to screen, diagnose and manage care for individuals at the mild AD, MCI or preclinical stage and to differentiate patients with dementia due to other causes .

BACKGROUND

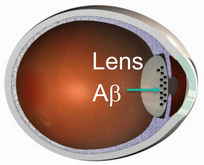
Goldstein *et al.* demonstrated the presence of Aβ deposits in the supranucleus (SN) of the lens of the eye in a population in whom AD had been confirmed by autopsy and differentiated from control samples [9].

Several studies have been focused on detecting b-amyloid in the eye as a technique to aid in the diagnosis of AD in humans [10-16]

The Normal Eye



The AD Eye



Cognoptix has developed a b-amyloid specific office-based eye test, Sapphire II, with demonstrated ability to distinguish between normal subjects and subjects with probable AD ([14]. Those results showed greater sensitivity and specificity than b-amyloid PET scans compared to clinical diagnosis.

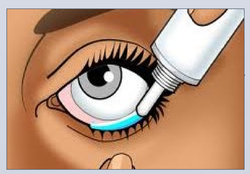
The Sapphire II system is a combination of a medical imaging ointment, applied to the lower eye lid, and a Fluorescent Laser Eye Scanning device. The eye is scanned to detect a highly specific shifted fluorescent signature signal of the medical imaging ointment bound to b-amyloid. Each scan takes less than a second and multiple readings can be obtained in a single sitting.

OBJECTIVES OF STUDY

Sapphire II has demonstrated ability to distinguish between normal subjects and subjects with probable AD [14]. Those results showed greater sensitivity and specificity than b-amyloid PET scans compared to clinical diagnosis.

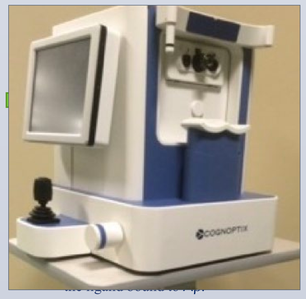
This study evaluates the utility of Sapphire II screening compared to b-amyloid PET scans in earlier MCI and Mild AD subjects.

Topical Administration



The fluorescent ligand is applied topically in the form of ointment which penetrates through the cornea into the anterior segments of the eye and specifically binds to Aβ.

Sapphire II : Fluorescence Signal



MATERIALS & METHODS

SAPPHIRE II System

The SAPPHIRE II system is a combination of a 1. *Fluorescent Ligand (Aftobetin),* formulated as a medical imaging ointment, applied to the lower eye lid, and 2. a Fluorescent Laser Eye Scanning *(SAPPHIRE II) Device*. The eye is scanned to detect a highly specific shifted fluorescent signature signal of the medical imaging ointment bound to b-amyloid. Each scan takes less than a second and multiple readings can be obtained in a single sitting.

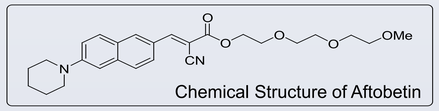
Fluorescent Ligand – Aftobetin

Aftobetin is a fluorescent compound that was designed according to the molecular rotor motif, which has been shown to bind to the aggregated Aβ peptide [13].

Chemical name: (E)-2-(2-(2-methoxyethoxy)ethoxy) ethyl-2-cyano-3-(6-(piperidin-1-yl)naphthalene-2-yl)acrylate

Formulated at 0.5% into an ophthalmic ointment consisting of 80% petrolatum and 19.5% mineral oil for topical application.

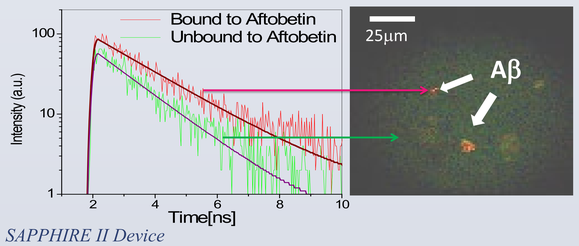
Demonstrated increase of fluorescence intensity by at least two folds upon binding to amyloid peptides.



Chemical Structure of Aftobetin

In vitro binding properties to amyloid aggregates

In vitro experiments demonstrate that bound and unbound peptide to Aftobetin can be resolved and differentiated with 0.85nsec difference in lifetime and at a detection level of few hundred photons.



SAPPHIRE II Device

SAPPHIRE II is a laser scanning device that comprises of fluorescence lifetime technique which is based on short pulse excitation repetitively and recording the subsequent fluorescence light emission as a function of time The fluorescence decay rate is then obtained for each location scanned in the human lens and the frequency counts of photons with specific decay lifetime (*i-photons/sec)* are calculated.

CLINICAL TRIAL: Pre-pivotal Studies for Safety and Efficacy Assessment

Clinical Trial : Study Design and Participants

Dose Administration

Three administrations of ointment consisted of a ½ inch ribbon (approximately 0.05 cc) of Aftobetin Ointment (0.5% concentration) topically administered to the inside of the lower eyelid with a syringe applicator. The timing of ointment administration was 1.5- 2 hours apart.

Method: 48 participants; 28 MCI, 16 Mild AD patients and 4 Normal subjects were studied. All MCI and AD subjects underwent cognitive testing and b-amyloid PET scans.

Measurement Sessions

Scans will occur at baseline (prior to ointment administration) and at 24 (+/- 2 hours), 28 (+/-30 minutes), and 48 hours (+/- 2 hours) after the first ointment administration.

RESULTS

Safety

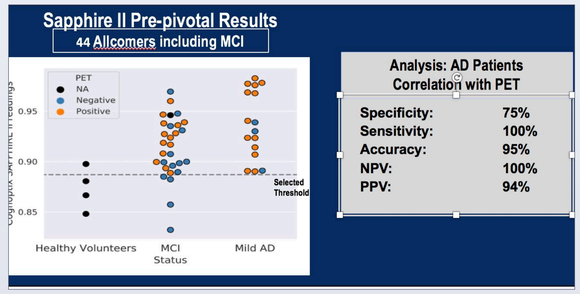
No serious adverse events were reported. 43 subjects have been evaluated thus far. The SAPPHIRE II System, device and ophthalmic ointment, used in this study posed no safety risk.

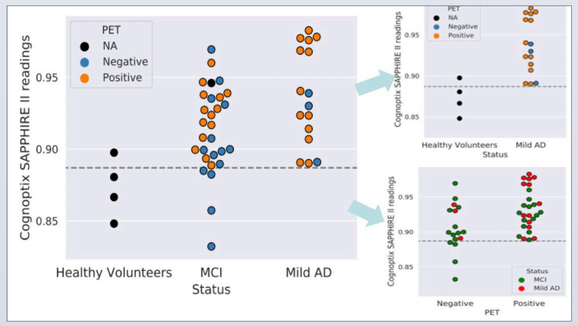
Efficacy

There was no instance where Sapphire II was negative and b-amyloid PET scans were positive – indicative of a high degree of specificity. Of the 39 Sapphire II positive subjects, positive b-amyloid PET scans were noted in 26. Evaluation of individual PET scans and cognitive testing suggests that Sapphire II is more sensitive than PET compared to clinical criteria.

correlation with cognitive testing and b-amyloid PET scans will be presented

Pre-Pivotal Results: All-comers' including MCI





- The clinical study was conducted with no serious adverse events related to the use of the fluorescent ligand, Aftobetin, or the laser scanning device in the eye.
- Evaluation of individual PET scans and cognitive testing suggests that Sapphire II is more sensitive than PET compared to clinical criteria.
- Sapphire II pre-pivotal data show strong correlation with PET Scanning in mild AD and MCI with possibly higher sensitivity than PET in MCI patients.
- No Patients Sapphire negative and PET Positive, some Sapphire positive but PET Negative
- **Mild AD:** 16 of 16 Mild AD Sapphire II pos, plus 3 Sapphire II positive, PET Negative
- **MCI:** 25 of 29 MCI Sapphire II pos; 10 patients Sapphire II positive, PET negative
- **Healthy Volunteers (HV)**V One healthy volunteer Sapphire positive, possibly pre-symptomatic/prodromal patient, now under further investigation
- 13 of 17 PET neg MCI & Mild AD patients read positively on Sapphire II

– Indicative of higher sensitivity; Improved Rule "in"

DISCUSSION

The data in this PRE-pivotal study complement the previous Phase II studies of detecting the presence of Aβ in the supranuclear region in lens samples from AD patients.

The results of this study are consistent with the prior Phase II study comparing Sapphire II data with PET in mild AD patients.

A total of 86 patients have been in both Phase II clinical studies combined. Pivotal studies as are planned as the next step.

Sapphire II is may be able to differentiate patients with dementias due to other causes.

The SAPPHIRE II System as a probable tool to screen for Alzheimer's disease at an early stage, at the MCI or at an even earlier prodromal asymptomatic stage.

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