2. LFBC Synopsis

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Clinical Study Report Synopsis: Study H6L-MC-LFBC

Title of Study: Effect of LY450139, a γ-Secretase Inhibitor, on the Progression of Alzheimer's Disease as Compared with Placebo

Number of Investigator(s): This multicenter study included 122 principal investigators.

Study Center(s): This study was conducted at 122 study centers in 18 countries.

Publication Based on the Study: None at this time.

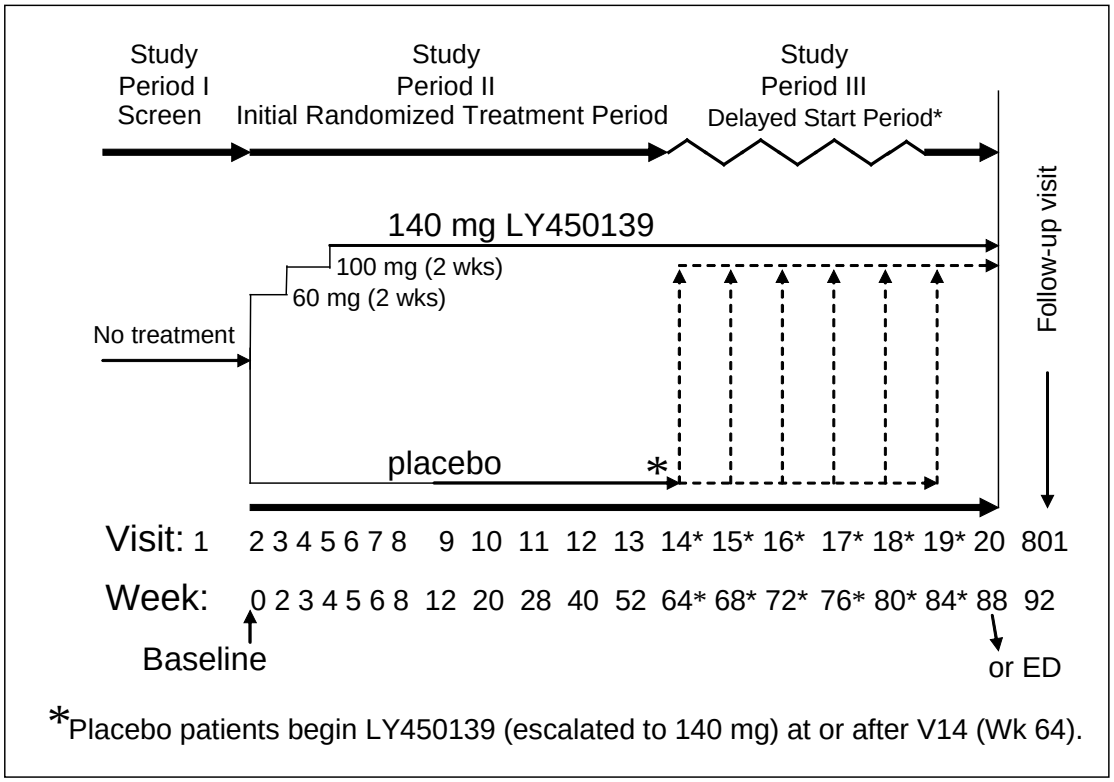
Length of Study:	**Phase of Development:** 3
First patient enrolled (assigned to therapy): 06 October 2008 Date of early study drug dosing cessation: 17 August 2010 Last patient completed: 26 April 2011	

Objectives: Semagacestat has a novel mechanism of action as a functional inhibitor of γ-secretase with the ability to inhibit the synthesis of amyloid-β (Aβ) potentially slowing the underlying rate of disease progression. The primary objective of this study was to test the hypothesis that semagacestat given orally would slow the decline of AD as compared with placebo. The primary objective was assessed using a mixed-model repeated measures (MMRM) analysis of 2 coprimary outcomes, the Alzheimer's Disease Assessment Scale—Cognitive subscore ($ADAS\text{-}Cog_{11}$) and the Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL), in which the specific hypothesis was that the change at the end of the initial treatment phase for semagacestat would be significantly less than that for placebo. This was evaluated at Week 76 of the 88-week trial, but investigators and patients were blinded to the timing of the primary endpoint. The secondary objectives of the study were: 1) to test the hypothesis that semagacestat is a disease-modifying medication independent of acute symptomatic effects using a "delayed-start" study design in which placebo patients began receiving double-blind semagacestat after 76 weeks in the study. The timing of the delayed start was blinded to investigators and patients; they were informed only that "sometime after 64 weeks," all patients would receive active semagacestat treatment; 2) to provide supporting evidence that semagacestat is a disease-modifying compound by assessment of multiple biomarkers; 3) to compare the safety of semagacestat and placebo; 4) to characterize population pharmacokinetics (PK) of semagacestat, explore potential factors that may have influenced variability of PK, and explore the association of PK variables with efficacy, biomarkers, and safety parameters; 5) to test the hypothesis that semagacestat would slow the rate of decline of AD using extended versions of the $ADAS\text{-}Cog_{11}$ and the Mini-Mental State Examination (MMSE) compared with placebo; and, 6) to assess global clinical benefit of treatment with semagacestat.

Patients may have chosen to participate in the assessment of exploratory hypotheses relating to various biomarkers of disease progression.

Study Design: Study H6L-MC-LFBC (LFBC) was a multicenter, randomized, double-blind, placebo-controlled, Phase 3 study comparing semagacestat 140 mg and placebo in approximately 1100 patients with mild to moderate AD. Patients who met entry criteria were randomized in a 1:1 ratio (550 per treatment arm) to 1 of 2 treatment groups: semagacestat 140 mg once daily or placebo once daily. Patients were randomized by site and by mild or moderate Mini-Mental State Examination (MMSE) scores (for the purposes of this study, moderate was defined as scores including 16 through 19, and mild as including 20 through 26). The primary hypothesis being tested was that semagacestat would slow the rate of cognitive and functional decline in AD as compared with placebo.
In addition, sometime after 64 weeks of treatment, patients receiving placebo began receiving semagacestat (escalated to 140 mg/day) for the remainder of the study. This "delayed-start" design feature evaluated whether patients originally treated with placebo improved during this period such that their cognitive scores subsequently approximated those of the patients initially treated with semagacestat. The absence of such an improvement—in other words, maintaining a statistical difference between patients initially assigned to semagacestat and placebo following the delayed start—would have supported the conclusion that semagacestat slows disease progression and did not affect simply symptoms of disease. Patients and investigators were blinded to the timing of the delayed start of active treatment for the placebo-treated patients.

The study design is shown in the figure below.



Abbreviations: ED = early discontinuation; wk = week

Number of Patients:
Planned: 1100 Actual: 1111
Randomized: 556 semagacestat 140 mg, 555 placebo
Completed: 22 semagacestat 140 mg, 34 placebo

Diagnosis and Main Criteria for Inclusion: Patients must have met National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD, had a Modified Hachinski Ischemia Scale score of ≤4, had an MMSE score of 16 through 26 at Visit 1, had a Geriatric Depression Scale (GDS) score of ≤6 (on the staff-administered short form), had a magnetic resonance imaging (MRI) or computerized tomography (CT) scan within the past 2 years on file with the investigator with no findings inconsistent with a diagnosis of AD, and have been at least 55 years old. If female, were post-menopausal, as evidenced by a lack of menstruation for at least 12 consecutive months or by having had a bilateral oophorectomy. Concurrent treatment with cholinesterase inhibitors or memantine was permitted if doses remain stable throughout the study. The full list of inclusion/exclusion criteria may be found in the Site Identification Questionnaire.

Study Drug, Dose, and Mode of Administration: Semagacestat, taken orally (preferably in the morning), starting at 60 mg once daily for 2 weeks and then escalating to 100 mg once daily; patients were escalated again to 140 mg once daily after taking 100 mg once daily for 2 weeks. At any point after Week 4 (Visit 5) of the study (when patients randomized to semagacestat are taking 140 mg once daily or 100 mg once daily), patients were allowed to dose-reduce (from 140 mg/day to 100 mg/day or from 100 mg/day to 60 mg/day) in the case of AEs that appeared to be drug-related and that, in the opinion of the site PI, would not have allowed continued participation in the study. Each patient received 3 tablets per day.

Reference Therapy, Dose, and Mode of Administration: Because the semagacestat dose strengths were a different size and color, a "triple-dummy" design was used, in which patients received placebo tablets with semagacestat tablets to match the strength(s) that was/were not being dosed. Each patient received 3 tablets per day.

Duration of Treatment:

Semagacestat Frequency: 88 weeks

Placebo Frequency: 64 weeks – followed by escalation to semagacestat 140 mg once-daily for 24 weeks

Variables:

Safety: Adverse events were collected at every visit, regardless of relationship to study drug. These events were captured as actual terms and coded to Medical Dictionary for Regulatory Activities (MedDRA) terms. Routine physical, skin and neurological examinations, including fundoscopy, were performed. Vital signs (including temperature) were taken at all visits, with blood pressure and pulse measured supine and standing at designated visits and sitting only at all other visits. Twelve-lead ECGs were obtained in triplicate. Laboratory evaluations, including chemistry, hematology, special hematology, special drug monitoring (for patients taking certain concomitant medications), and urinalysis panels, were collected at regular intervals.

Efficacy: The Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS- Cog_{11}) and Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) cognitive testing instruments were used as primary measures in this study. Secondary clinical outcome measures included: The Clinical Dementia Rating Scale (CDR); Neuropsychiatric Inventory (NPI); Resource Utilization in Dementia—Lite questionnaire (RUD-Lite); the EuroQoL-5D (EQ-5D) Proxy; and, Mini-Mental State Examination (MMSE). Plasma samples for assessment of Aβ were collected from all patients. Patients may have chosen to participate in the assessment of additional biomarkers, including FDG-PET, vMRI, amyloid imaging and CSF via study addenda. Information about these assessments is provided in the addenda.

Bioanalytical: Blood samples were collected to measure the concentration of donepezil, study drug, and study drug metabolites (as appropriate).

Pharmacokinetic: All plasma semagacestat concentration-time data was pooled and evaluated by a population PK approach. A covariate screen of patient-specific factors was included in the analyses based on those factors investigated in previous and ongoing PK analyses and those appropriate for the target population. An exploratory analysis to investigate a relationship between plasma semagacestat and the proximal secondary endpoint (plasma Aβ) at Weeks 0, 12, and 52 was also conducted. Other analyses of efficacy and safety outcome measures may also have been assessed as scientifically appropriate and warranted by available data.

Evaluation Methods:

Statistical: The primary objective of this study was to test the hypothesis that semagacestat given orally would slow the decline of AD as compared with placebo. The primary objective was assessed using a mixed-model repeated measures (MMRM) analysis of 2 coprimary outcomes, the Alzheimer's Disease Assessment Scale—Cognitive subscore (ADAS-Cog_{11}) and the Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL), in which the specific hypothesis is that the change at the end of the initial treatment phase for LY450139 will be significantly less than that for placebo. Change from baseline difference in the MMSE scores was also analyzed using a repeated measures mixed model analysis.

Safety: Safety was assessed by summarizing and analyzing TEAEs, laboratory analytes, vital signs, and ECGs. Unblinded data on safety-related endpoints and SAEs were periodically reviewed by the Data Monitoring Committee (DMC). In addition, for safety reasons, the DMC evaluated ADAS-Cog results after approximately 50% of the patients had at least 12 months of treatment. A blinded Clinical Endpoint Committee (CEC) reviewed and adjudicated specific safety endpoints.

Summary and Conclusions:

Semagacestat is a gamma secretase inhibitor that was being studied in two pivotal Phase 3 clinical trials (LFAN and LFBC) to determine effectiveness in slowing the progression of AD by decreasing the production of suspected neurotoxic species of amyloid beta peptide. During a protocol pre-specified interim analysis for cognitive safety in LFAN, the external DMC discovered statistically significant dose-dependent cognitive and functional worsening in semagacestat-treated patients compared with placebo-treated patients. Dosing with semagacestat was halted in both

Phase 3 trials and the open label extension study. Patients were given the option to continue in the respective amended studies to have their cognition, function and traditional safety measures assessed for an additional 7 months after dosing cessation.

Because study LFBC started approximately 6 months after Study LFAN, fewer patients were available for analysis when semagacestat dosing was halted. In addition LFBC allowed greater flexibility for dose decreases than LFAN. Thus, although LFBC results are consistent with those of LFAN, they do look slightly different. For example, whereas the cognitive and functional worsening was numerically worse (at most time points) in semagacestat versus placebo patients in Study LFBC, cognitive and functional worsening was statistically significantly worse in LFAN.

In LFAN, the cognitive and functional decline of patients initially treated with semagacestat was not different than patients initially treated with placebo in the 7 month Safety Follow-Up Period, suggesting that semagacestat treated patients did not continue to worsen beyond what is expected for mild to moderate AD patients after dose cessation. However, cognition and function did not return to placebo levels and therefore were not "reversed" during the Safety Follow-Up Period. This is also true for the functional measure (ADCS-ADL) in the Safety Follow-Up Period of LFBC, but the cognitive measure ($ADAS\text{-}Cog_{11}$) suggests that, in LFBC, semagacestat and placebo patients' scores may have come back together (i.e., the cognitive worsening in the initial treatment period "reversed").

In addition, in LFBC, a significant interaction existed between change in ADCS-ADL and study drug compliance, suggesting that only those patients who were not compliant with active study drug were worse in function than placebo patients. The reasons for this inconsistency are unclear but there were more semagacestat patients who were non-compliant than placebo patients, likely related to the higher incidence of TEAEs necessitating drug holidays.

From a safety perspective, the findings in LFBC were quite similar to LFAN but some significance was lost at the later visits due to smaller sample size. Like LFAN, most of the findings in the LFBC study were predicted by earlier toxicology and pre-clinical studies and with Phase 1 healthy volunteer pharmacology studies and Phase 2 clinical studies in patients with AD. These studies suggested the possibility for QTc prolongation, induction of donepezil metabolism and other drugs metabolized by CYP3A4/5, gastrointestinal effects, rash, hair and skin depigmentation, renal tubular effects and hepatic enzyme elevations. However, in large part due to the brevity of the earlier studies, AEs that might require longer exposure to manifest were not identified. For example, rates of infection and neoplasms were not elevated with semagacestat treatment in toxicology studies or Phase 1 or 2 studies. Also weight loss was not identified as a risk, though again, exposures were not of sufficient length to see such changes.

A detailed description of the potential mechanisms of the safety findings with semagacestat is beyond the scope of this document, but several key points are of note. First, there are multiple substrates for gamma secretase and inhibition of cleavage of (and therefore decreased signaling of) one or more of these may have led to these findings. At the time semagacestat was discovered, only the transmembrane protein Notch was known to be an alternate substrate for gamma secretase (in addition to APP). There are a multitude of data now on the effects of Notch signaling and the inhibition thereof. In fact, the literature suggests that inhibiting Notch signaling may lead to altered hematopoiesis (altering numbers of immune cells such as B- and T-lymphocytes and increasing rates of infection), effect cell differentiation including of melanocyte stem cells into melanoblasts and melanocytes (leading to lack of melanin in hair and skin and therefore depigmentation), and differentiation of GI epithelial cells (leading to goblet cell hyperplasia and diarrhea), increase keratinocyte proliferation (which, when combined with environmentally induced mutations, allows these mutations to accumulate and increases the rate of squamous cell and basal cell carcinoma of the skin), and decreased differentiation of monocytes into dendritic cells (known as Langerhan cells in skin which could increase rates of skin infection and perhaps increase circulating monocyte counts). There are several reviews of Notch signaling and its effect in the pathogenesis of skin diseases and its effect in tumorigenesis and tumor suppression.

While some of the safety findings with semagacestat may be explained by inhibiting Notch cleavage, the mechanisms underlying other safety findings remain unclear. For example, the mechanism for the effect on renal tubular reabsorption that could explain decreases in phosphorus, uric acid, potassium and calcium and glycosuria remains a mystery. Also, the mechanism behind the rashes seen with semagacestat is also unclear. Finally, the mechanism behind the increased hepatic enzymes such as ALT, AST and GGT could be an adaptive response of the liver to semagacestat, but the etiology of the decreases in bilirubin also remains a mystery.

Finally, the mechanism underlying the cognitive and functional worsening seen with semagacestat remains unknown. Several possibilities exist, including effects on levels of fragments normally produced by cleavage of APP by gamma secretase such as amyloid precursor protein intracellular domain (AICD) (decreased with γ-secretase inhibition) or the c-terminal 99 amino acid fragment of APP (c99) (increased with γ-secretase inhibition). AICD may have involvement in gene transcription, apoptosis, development and cytoskeletal dynamics. Other possible explanations for the cognitive and functional worsening seen with semagacestat treatment include the apparent increase in Aβ1-42/1-40 ratio, inhibition of Notch signaling, and/or inhibition of another substrate of gamma secretase. One other known substrate with data to suggest a role in cognition is EphA4. Gamma secretase is responsible for cleavage of EphA4 to produce and intracellular domain (EICD), which is responsible for neuronal synaptic plasticity when environmental stimulus is applied. Inoue and colleagues demonstrated that a γ-secretase inhibitor was associated with decreased EICD and decreased dendritic spine density. Additionally, Bittner and colleagues demonstrated that semagacestat decreased dendritic spine density in wild-type mice but not in APP-deficient mice suggesting that the decrease in dendritic spine density was mediated by APP.

In conclusion, semagacestat was being studied as a potential disease modifying therapy for AD and had a robust biomarker signature leading into Phase 3 development. Dosing was halted early in this phase 3 study, however, due to greater rates of cognitive and functional decline in the semagacestat treated patients compared to placebo treated patients. Patients were followed to assess reversibility of the worsened cognition and function and of traditional safety measures. While the rates of cognitive and functional decline for patients previously taking semagacestat were not different than for patients previously taking placebo in the 7 month Safety Follow-Up Period, cognitive function was not statistically different between the two groups at the end of the Safety Follow-Up Period. Functional abilities did not return to placebo levels. However, with a few exceptions, the effects of semagacestat on traditional safety findings were reversed once dosing was discontinued. Importantly, the rate of skin cancer with previous semagacestat exposure was the same as placebo in the follow-up period suggesting that patients exposed to semagacestat did not have permanently increased risk for skin cancer.