2. LFBF Synopsis

Approval Date: 13-Mar-2012 GMT

Clinical Study Report Synopsis: Study H6L-MC-LFBF

Title of Study: Open-Label Extension for Alzheimer's Disease Patients Who Complete One of Two Semagacestat Phase 3 Double-Blind Studies (H6L-MC-LFAN or H6L-MC-LFBC)

Number of Investigator(s): At the time semagacestat dosing was stopped, 71 principal investigators had enrolled patients.

Study Center(s): At the time semagacestat dosing was stopped, 71 study centers in 14 countries had enrolled patients.

Publication(s) Based on the Study: None at this time.

Length of Study:
First patient enrolled (assigned to therapy): 29 December 2009
Date of early study drug dosing cessation: 17 August 2010
Last patient completed: 08 April 2011

Phase of Development: 3

Objectives: The primary objective of the study was to assess the safety of semagacestat in Alzheimer's disease (AD) patients during 24 months of open-label treatment following completion of up to 21 months of active treatment in a double-blind registration study (LFAN or LFBC) through analysis of adverse events (AEs), vital signs, laboratory evaluations, and electrocardiograms (ECGs). The secondary objectives of the study were: 1) to test the hypothesis that semagacestat would continue to slow the cognitive and functional decline associated with AD during 24 months of open-label treatment; 2) to assess global clinical benefit of treatment with semagacestat during 24 months of open-label treatment; 3) to provide up to 24 months of additional efficacy data in patients who were initially randomized to placebo in the registration studies and who initiated semagacestat during the delayed-start portion of the registration studies; and, 4) to provide evidence that semagacestat continues to reduce Aβ in plasma within 6 hours of administration during long-term treatment.

Patients who participated in the vMRI and/ or Amyloid Imaging Addendum of the registrations studies had the option to participate in the same addenda in Study LFBF

Study Design: This was a 24-month, open-label, single-arm extension study in patients with AD who completed 1 of 2 Phase 3 double-blind registration studies (LFAN or LFBC). At Visit 1, patients entered a 2-week blinded lead-in so that those taking 60 mg or 100 mg semagacestat at the end of the double-blind study could be titrated to 140 mg while maintaining the blind of the previous study. At Visit 2, all patients were assigned open-label semagacestat 140 mg daily. Dose reductions to 100 mg or 60 mg daily due to intolerable AEs may have occurred after Visit 2.

Number of Patients:
Planned: 1500 Actual: 188
Completed: No patients completed the study as semagacestat dosing was stopped approximately 8 months after enrollment started.

Diagnosis and Main Criteria for Inclusion: Alzheimer's disease patients who completed 1 of 2 Phase 3, double-blind registration studies (LFAN or LFBC) were eligible to participate in this study providing they did not meet any discontinuation criteria. Patients were to be enrolled into this extension study on the day that they completed the Phase 3 study.

Study Drug, Dose, and Mode of Administration:
Semagacestat 140mg, once daily, orally, with an option to reduce dose to 100 mg or 60 mg once daily due to intolerable adverse events.

Reference Therapy, Dose, and Mode of Administration: Not applicable.

Duration of Treatment:
Planned Treatment Period: 24 months

Variables:

Safety: Treatment-emergent adverse events (TEAEs) were collected at every visit, regardless of relationship to study drug. Routine physical, skin and neurological exams were performed and vital signs (pulse, blood pressure, temperature), weight, laboratory analytes, and ECG data were collected.

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). Patients may have chosen to participate in the assessment of additional biomarkers (vMRI and amyloid imaging) if they had done so in the registration study.

Pharmacokinetic: Plasma samples for assessment of semagacestat concentrations were obtained at Visit 4.

Pharmacodynamic: Plasma samples for assessment of Aβ concentrations were obtained at Visit 4.

Evaluation Methods:

All analyses were performed on an intent-to-treat (ITT) basis unless otherwise specified. Because so few patients from LFBC (N=8) were enrolled into LFBF prior to dosing cessation, this clinical study report contains data only from patients who completed LFAN (N=180). Treatment groups used in the LFBF statistical analysis were the treatment groups to which the patients were randomized in LFAN:

1. LFAN Placebo – patients who were randomized to placebo in the LFAN initial treatment period, then were titrated to 140 mg semagacestat in the LFAN delayed start period (3 months with no option for dose reduction). These patients stayed on LY140 during the 2 week LFBF titration period but could dose reduce after that point to 100 mg or 60 mg.
2. LFAN LY100 – patients who were randomized to LY100 mg in the LFAN initial treatment period. These patients were allowed to dose reduce to 60 mg for intolerable AEs during the initial treatment period and remained on their initial treatment period dose (100mg or 60mg) throughout the delayed start period. These patients were titrated to LY140 during the LFBF titration period and were required to remain on 140 mg for 2 weeks, at which time they could dose reduce to 100mg or 60mg. This group had the shortest exposure to LY140.
3. LFAN LY140 – patients who were randomized to LY140 mg in the LFAN initial treatment period. These patients were allowed to dose reduce to 100 mg for intolerable AEs during the initial treatment period and remained on their initial treatment period dose (140 mg or 100 mg) throughout the delayed start period. These patients either remained at 140 mg or were titrated to 140 mg during the LFBF titration period and were required to remain on LY140 for 2 weeks, at which time they could dose reduce to 100 mg or 60 mg.

Summary and Conclusions:

Semagacestat is a gamma secretase inhibitor that was being studied in 2 pivotal Phase 3 clinical trials (Study LFAN and Study 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 the LFAN Study, the external Data Monitoring Committee (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 this 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.

During the LFBF Safety Follow-Up Period after dosing cessation, patients in the LFAN placebo group showed cognitive and functional improvement on ADAS-Cog_{11} and ADCS-ADL scores whereas patients in the LFAN LY100 and LFAN LY140 groups continued to decline, possibly because the LFAN placebo patients had the shortest exposure to semagacestat.

From a safety perspective, all of the findings in the LFBF study were predicted by the pivotal Phase 3 studies and no new safety concerns were identified. Because all the patients in LFBF had already been exposed to semagacestat treatment for at least 3 months, no clear placebo comparisons can be made and, in general, the types of TEAEs, serious adverse events (SAEs), and discontinuations due to TEAEs were the same as in study LFAN. Taken together with the Phase 3 study data, semagacestat treatment appears associated with several categories of TEAEs (gastrointestinal, rash, non-melanoma skin cancer, skin/hair hypopigmentation, infections, and metabolic changes), changes in many lab analytes, increases in QTc, and decreases in weight. Since there was no true placebo group with which to compare semagacestat groups with in the LFBF Safety Follow-Up Period, interpretations of reversibility of safety data was not possible. But, based on the safety follow-up periods of Phase 3 studies, with few exceptions, safety related effects of semagacestat reversed at variable time points during this 32-week treatment period.

Caution in interpreting the data is warranted. For example, because the dosing with semagacestat was halted mid-study, the semagacestat exposure times across and within treatment groups varied widely. In addition, fewer LFAN LY140 patients continued into LFBF since more patients randomized to the LY140 treatment group discontinued due to a TEAE in LFAN. Arguably, those that did continue into LFBF may have been a more tolerant group. They had less SAEs overall (LFAN LY100 and LFAN placebo groups both had more SAEs) but more TEAEs than the other groups.

Another consideration in interpreting the LFBF data is that while the LFAN LY100 treatment group had more exposure to semagacestat than LFAN placebo patients, they had the shortest exposure to the 140mg dose due to remaining on 100mg during the LFAN delayed start period. Despite these differences between the groups, their TEAE profiles were similar. However, for many of the lab, ECG, and vital sign measures, the LFAN LY100 group had less change or incidence of abnormality. This may be due to their shorter exposure to the 140mg dose of semagacestat. Interestingly, this treatment group also had the longest time to all cause discontinuation in LFBF and no discontinuations due to TEAEs.

Finally, of particular note is that the mean change analyses for laboratories, vital signs, and ECG parameters appear to be “opposite” of the findings in LFAN. For example, CD19 absolute counts showed mean increases, QTcF showed mean decreases, uric acid showed mean increases, etc. This was likely an artifact of using Visit 1 of LFBF as baseline in these analyses (ie. all patients were already on semagacestat). A bulleted summary of the efficacy and safety findings from LFBF is found in the Conclusions section of this report and descriptions of the potential mechanisms of the safety findings can be found in the full LFAN and LFBC Clinical Study Reports. In addition, although the mechanism underlying the cognitive and functional worsening seen with semagacestat remains unknown, several possible mechanisms are discussed in the full LFAN and LFBC Clinical Study Reports.