1 Study Synopsis

Name of Sponsor/Company:	Lexicon Pharmaceuticals Incorporated
Name of IMP:	LX6171 Oral Suspension
Name of Active Ingredient:	LX6171

Title of Study: A Randomized, Double-blind, Placebo-controlled Study to Determine Safety and Tolerability of LX6171 Oral Suspension Dosed for 28 Days in Subjects Exhibiting Age Associated Memory Impairment (AAMI), with a Lead-in, Open-label, Single-dose Relative Bioavailability Study of LX6171 Oral Suspension in Healthy Elderly Subjects.

Investigators: Principal Investigator: Huub van Paaschen, MD, Kendle International. Investigator: Renger Tiessen, MD, PRA International Group BV.

Study Center(s): The study was performed at 2 study centers in the Netherlands: Site 1 in Utrecht, and Site 2 in Zuidlaren.

Publication (Reference): None.

Studied Period:	**Phase of Development:**
• First subject first visit: 15 Nov 2007 • Last subject last visit: 23 Oct 2008	Phase IIa

Objectives:

Stage A: The primary objectives were:

- To compare the relative bioavailability of a single dose of 300 mg LX6171 using a 40 mg/mL and an 80 mg/mL formulated suspension;
- To evaluate plasma concentrations of LX6171, and its major metabolite LP-523122 after a single 300 mg administration of LX6171 oral suspension at 2 concentrations (40 mg/mL and 80 mg/mL), in order to determine doses to be utilized over a 28 day period (see Stage B).

The secondary objective was:

- To evaluate the safety and tolerability of single doses of 300 mg of LX6171 utilizing two different concentrations of oral suspension (40 mg/mL and 80 mg/mL) in healthy elderly subjects

Stage B: The primary objective was:

- To evaluate the safety and tolerability of 2 dose levels LX6171 oral suspension when administered for 28 days, in subjects exhibiting AAMI

The secondary objectives were:

- To evaluate effects of multiple doses of LX6171 oral suspension on cognition in subjects exhibiting AAMI
- To evaluate plasma concentrations of LX6171 and its major metabolite LP-523122 after administration of LX6171 oral suspension for 28 days, in subjects exhibiting AAMI

Methodology:

This was a 2-stage proof-of-concept study to determine the safety, tolerability, and effects on cognition of multiple doses of LX6171 oral suspension, in subjects exhibiting AAMI,

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following an initial lead-in relative bioavailability evaluation in healthy elderly subjects.

Stage A: Stage A was an open-label, single-dose relative bioavailability evaluation. Sixteen healthy elderly subjects (60 to 80 years old) were given a single dose of 300 mg LX6171 in either a 40 mg/mL or 80 mg/mL suspension. The subjects were confined to the study center from Day -1 until the morning of Day 3. Serial blood samples were drawn for PK analyses and safety and tolerability were assessed. After being discharged from the unit, subjects visited the study center on Day 7 and 14 for collection of plasma PK samples. At the end of Stage A, using unaudited pharmacokinetic (PK) plasma data from Day 1 to Day 3 the relative bioavailability, and the tolerability of the 2 dose concentrations was evaluated to determine 2 dose levels, to be used in Stage B, the putative clinical dose level and half of that dose.

Stage B: Stage B was a randomized, double-blind, placebo-controlled, proof-of-concept study assessing the safety, tolerability and effects on cognition of 2 different dose levels of LX6171 oral suspension over a 28 day dosing period, in subjects exhibiting AAMI. One hundred-and-twenty (120) elderly subjects (60 to 80 years old), exhibiting AAMI were dosed once daily with either a low or a high dose of LX6171 or matching placebo (40:40:40 subjects). The high dose (using the 80 mg/mL suspension) was selected on the basis of the data obtained from Stage A, using PK modeling and compartmental simulations to target mean peak plasma levels of approximately 6,000 ng/mL. The low dose was achieved using the 40 mg/mL suspension delivered at a volume equal to the high dose, in order to maintain the blinding.

An interim blinded safety and plasma concentration review was performed after 18 subjects had completed Day 28 of the study (6 high dose, 6 low dose, and 6 placebo) before continuing enrolment into the study.

On Day -1, subjects visited the study center for baseline assessments and to be supplied with investigational medicinal product (IMP). On Day -1 the subjects were trained on how to prepare and administer the IMP. The subjects were instructed to take the IMP once daily, at approximately the same time of day, within 30 min of starting breakfast on days that they did not visit the clinic. Subjects kept a diary, where they recorded the time and date of IMP intake and breakfast. Subjects returned to the center for weekly assessments. At each visit a blood sample for PK analyses was drawn and safety, tolerability and cognition were assessed. At the Day 35 Follow-up Visit, one last blood sample was drawn for PK analyses. Protocol Amendment 3, (dated 24 Mar 2008) clarified that Stage B was to be conducted in 2 parts, Stage B1 (the initial 18 subjects) and Stage B2 (the remaining subjects).

Number of Subjects (Planned and Analyzed):

It was planned that 136 subjects would be enrolled in the study: 16 subjects in Stage A, and 120 subjects in Stage B (18 subjects in Stage B1 and 102 in Stage B2). Sixteen (16) subjects were enrolled in Stage A and 121 subjects were enrolled in Stage B (18 subjects in Stage B1 and 103 subjects in Stage B2).

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Diagnosis and Main Criteria for Inclusion and Exclusion:
Stage A: Male or female subjects between 60 and 80 years of age, with a systolic pressure of 100 to 140 mmHg, a diastolic pressure of 60 to 100 mmHg and with no known history of significant hepatic disease or hematological abnormalities.
Stage B: Male or female subjects between 60 and 80 years of age and exhibiting AAMI with a systolic pressure of 80 to 150 mmHg, diastolic pressure of 60 to 100 mmHg and no known history of myocardial infarction within 12 months before enrolment in the study.

Test Product, Dose and Mode of Administration, Batch Number:
LX6171 was supplied as a 40 mg/mL suspension and an 80 mg/mL suspension. Subjects in Stage A of the study received a single oral dose of 300 mg of LX6171 as either a 40 mg/mL suspension (Lot Number C1248A001), or 80 mg/mL suspension (Lot Number C1246A001).
Subjects in Stage B of the study received a single oral dose of LX6171 as a high dose (160 mg) or a low dose (80 mg), or a single oral dose of placebo once daily for 28 days. The high dose (using the 80 mg/mL suspension [Lot Number C1246A001]) was selected using data from Stage A. The low dose was achieved using the 40 mg/mL suspension (Lot Number C1248A001) administered at a volume equal to the high dose. An interim blinded safety and plasma concentration data review was performed after 18 subjects had completed Day 28 of the study (6 high dose, 6 low dose and 6 placebo) and a dose adjustment was made on the basis of this review. Subjects randomized to high dose LX6171 received 240 mg (using the 80 mg/mL suspension) and subjects randomized to low dose LX6171 received 120 mg LX6171 (using the 40 mg/mL suspension).

Duration of Treatment:
Stage A: The maximum study duration for each subject was 35 days, including a screening 21 days prior to admission to the Clinical Pharmacology Unit (CPU).
Stage B: The total maximum study duration for each subject was 63 days, including a screening 28 days prior to admission to the center and a Follow-up Visit 7 days after the last dosing.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Stage A: Not applicable.
Stage B: The matching placebo (Lot Number C1244A001) consisted of dosing vehicle only and was supplied as a solution. Placebo-treated subjects received the same volume of suspension as subjects dosed with LX6171.

Criteria for Evaluation:

Pharmacokinetics:
Stage A: PK plasma samples were collected in Stage A on Day 1A (predose, 0.25 h, 0.5 h, 0.75 h, 1 h, 2 h, 3 h, 5 h, 8 h, and 12 h post dose), Day 2A (16 h, 24 h post dose), Day 3A (36 h, 48 h post dose), Day 7A (144 h post dose) and Day 14A (312 h post dose).
Stage B: PK plasma samples were collected in Stages B1 and B2 on Day -1B1 and Day -1B2 at pre-dose (+/- 1 day) on Days 7B1/B2, 14B1/B2, 21B1/B2 and 28B1/B2, and

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on Day 35 B1/B2.

Pharmacodynamic Assessments:

Stage A: No pharmacodynamic assessments were planned for Stage A of the study.

Stage B: A standardized, validated Computerized Cognitive Assessment System from Cognitive Drug Research (CDR), Memory Assessment Clinics Self-rating Scale (MAC-S); 15-word Test; One Word Delayed Recall Test (OWDRT); Epworth Sleepiness Scale (ESS); and Pittsburgh Sleep Quality Index (PSQI).

Safety & Tolerability:

Safety and tolerability were assessed by monitoring adverse events (AEs), laboratory test results (hematology, clinical chemistry, serology, and urinalysis), vital signs, (supine blood pressure, pulse rate and temperature), electrocardiogram (ECG) results, and physical examination.

Statistical Methods:

Pharmacokinetics:

PK parameter estimation, modelling and interpretation was performed by Charles River Laboratories. The following PK parameters were estimated for LX6171 and its main metabolite LP-523122, where possible, for each individual subject following single doses of either 40 mg/mL or 80 mg/mL oral suspension of LX6171: maximum observed plasma concentration ($Cmax_{(obs)}$); time at which Cmax was observed ($Tmax_{(obs)}$); area under the plasma concentration-time curve (zero to last measured concentration) ($AUC_{(0-t)}$); area under the plasma-concentration time curve (zero to infinity) ($AUC_{(0-\infty)}$); the terminal elimination half-life ($T_{1/2el}$); the metabolite formation half-life estimated by the model ($T_{1/2abs}$); the terminal elimination rate constant (kel); clearance (CL/F); the apparent volume of distribution (Vd/F); and relative bioavailability (Frel, %). A measured plasma concentration *vs* time curve was produced for each subject and analyte on both linear/linear and log_e/linear scales. Mean plasma concentration *vs* time curves were also presented for each analyte and treatment. Summary statistics (*ie* mean, median, SD, geometric mean, minimum, maximum, n and coefficient of variation) were calculated for plasma concentrations for each analyte, timepoint and treatment.

Summary statistics (*ie* mean, median, SD, minimum, maximum and n) were presented for all PK parameters by analyte and treatment. In addition, geometric means and coefficients of variation (CV_b) (based on the natural logarithmically transformed data) were presented for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$ and $Cmax_{(obs)}$. All plasma concentration and PK data were to be listed.

For Stage B, summary statistics (*ie* mean, median, SD, geometric mean, minimum, maximum, n and coefficient of variation) were to be calculated for plasma concentrations for each day, analyte, timepoint and treatment.

Pharmacodynamic Assessments (Stage B only):

Stage B: CDR analyzed the standardized and validated cognitive assessment battery and provided a full separate statistical analysis plan and report to document the outcome

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of the analysis. The report contained graphs of the data and listings of summary statistics, summary statistics for the difference from baseline data, summary SAS output and raw data.

MAC-S, 15-word Test, OWDRT, ESS, and PSQI data were analyzed by the Biometrics department of Kendle. Analysis of covariance (ANCOVA) was performed on the change from baseline for MAC-S, ESS, PSQI and 15-word Test using the relevant baseline value as the covariate. ANCOVA was performed for OWDRT using the previous weeks value as the covariate. Descriptive statistics were presented for the above parameters by treatment at each timepoint.

Safety:

Stage A: AEs, vital signs, clinical laboratory results, and ECG data were summarized together with presentations of abnormal findings, by dose concentration group. AEs were summarized within each study phase and overall study phases for each treatment group.

Stage B: AEs, vital signs, clinical laboratory results, and ECG data were summarized together with presentations of abnormal findings, by study phase separately at each timepoint by treatment group. AEs were summarized within each study phase and overall study phases for each treatment group.

Summary – Conclusions:

Pharmacokinetic Results:

Plasma concentration *vs* time curves for both LX6171 and its major metabolite LP-523122 were typified by moderately rapid absorption (and formation of metabolite LP-523122) with individual $Tmax_{(obs)}$ estimates ranging from 0.75 h to 3.00 h and from 2.00 h to 5.00 h for LX6171 and LP-523122, respectively. Thereafter, both analytes' concentrations generally declined in a bi-phasic manner, with LX6171 and LP-523122 quantifiable up to at least 144 h and 312 h (last sampling timepoint) after the start of dosing, respectively.

The estimate of relative bioavailability for the 40 mg/mL formulation relative to the 80 mg/mL formulation was 86.7% and 105.3% for LX6171 and LP-523122, respectively.

Estimates of relative bioavailability of LX6171 for the 40 mg/mL and 80 mg/mL suspension formulations dosed in this study compared to the solution formulation dosed in the previous Phase 1b study (LX6171.1-102-NRM) were 124.9% and 144.0%, respectively.

Estimates of relative bioavailability of LP-523122 for the 40 mg/mL and 80 mg/mL suspension formulations dosed in this study compared to the solution formulation dosed in the previous Phase 1b study (LX6171.1-102-NRM) were 251.5% and 238.8%, respectively.

Review of predose LX6171 and LP-523122 trough concentrations from Days -1, 7, 14, 21, 28 and 35 confirmed that steady state was reached by Day 21 or Day 28 in all subjects for both analytes.

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Pharmacodynamic Results:

Review of the results of pharmacodynamic assessments (cognitive assessments) showed that there was little evidence to support the hypothesis that LX6171 improves cognition in healthy elderly volunteers exhibiting AAMI, when administered as a daily oral dose for 28 days, in the dose range of 80 mg to 240 mg. Therefore, only key PD assessments were discussed in the text of this report.

Overall, the computerized cognitive assessment system results suggested little indication of an improvement or a decline in cognition and self-rated mood and alertness for LX6171. There was a suggestion that LX6171 may have improved the speed at which items were correctly recalled from memory (Speed of Memory). However, this improvement was only seen in one of the 3 subtasks contributing to the composite score at one timepoint. Isolated improvements *vs* placebo were seen in the intensity of attention (Power of Attention). On the other hand, declines *vs* placebo were seen in the ability to sustain attention (Continuity of Attention) and in the ability to maintain information by rehearsal in working memory (Numeric Working Memory). However, these improvements and declines were not consistent over cognitive domains, across dose levels, or over assessment days, and consequently were unlikely to be genuine effects of the study compound. In conclusion, there was little evidence from the computerized cognitive assessment system results in this study to support the hypothesis that LX6171 improves cognition in healthy elderly volunteers exhibiting AAMI, when administered as a daily oral dose for 28 days, in the dose range of 80 mg to 240 mg LX6171.

Over all days combined, statistical analysis of MAC-S total scores for Stages B1 and B2 combined showed a statistically significant improvement in change from baseline MAC-S total scores in the placebo treatment group compared with the low dose LX6171 treatment group (80 mg and 120 mg combined). This difference was apparent from Day 14 onwards and was greatest on Day 28. There were no other statistically significant differences between the low dose and high dose groups combined, or between the low dose group and the high dose group.

Over all days combined, there was no statistically significant treatment effect with respect to change from the baseline 15-word Test acquisition score or short-term delayed recall score for Stage B2. On Day 7 of Stage B2 there was a statistically significant increase in the 15-word Test acquisition score in the placebo treatment group compared with the 120 mg LX6171 treatment group, although this result should be interpreted with caution due to multiple testing.

There were no other statistically significant differences for any other comparison of treatment groups on any other day for the 15-word Test acquisition score or the short term delayed recall score.

Safety Results:

Stage A: No SAEs were reported during Stage A of the study, no subject died during Stage A and no subject was withdrawn from Stage A as a result of an AE.

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AEs were reported for a slightly higher proportion of subjects in the 40 mg/mL LX6171 treatment group than in the 80 mg/mL LX6171 treatment group (37.5% *vs* 25%). However, there was no difference between the 2 treatment groups in the proportion of subjects with IMP-related AEs (25% in each group). All AEs were considered to be mild in severity. No individual AE was reported for more than one subject (12.5%) in each treatment group. IMP-related AEs of diarrhea, nausea, headache, somnolence and leucocyturia were reported.

There were no notable median changes from baseline in any hematology or clinical chemistry parameter in either the 40 mg/mL LX6171 or 80 mg/mL LX6171 treatment group. With the exception of the QT interval, there were no notable mean changes from baseline in vital signs or ECG. There were a number of small median decreases in the QT interval in the 40 mg/mL LX6171 treatment group compared with baseline (Day -1) and small median increases in the QC interval in the 80 mg/mL LX6171 treatment compared with baseline (Day -1) at a number of timepoints after dosing. There were no changes in physical examination findings during Stage A of the study.

Stage B1: No SAEs were reported and no subject died during Stage B1 of the study. One subject (80 mg LX6171) was withdrawn from the study as a result of AEs of aspartate aminotransferase (AST) increased, considered to be of moderate severity, and blood creatine phosphokinase increased, considered to be severe. Both events were reported 12 days after the first dose of IMP and were considered to be possibly related to IMP. However, this subject also had elevated creatine kinase at baseline and in addition, the investigator commented that excessive physical exertion (with the potential for associated muscle injury) may have contributed to the AEs of AST increased and blood creatine phosphokinase increased in this subject.

AEs and IMP-related AEs were reported for fewer subjects in the 160 mg LX6171 treatment group (3 [50%] subjects and 2 [33.3%] subjects, respectively) than in the other 2 treatment groups. There was little difference in the proportion of subjects reporting AEs and IMP-related AEs in the 80 mg LX6171 treatment group (5 [83.3%] subjects for both AEs and IMP-related AEs) and the placebo treatment group (6 [100%] subjects and 5 [83.3%] subjects, respectively)

The majority of AEs were reported in a maximum of one (16.7%) subject in any treatment group.

The most commonly reported AEs in subjects in the placebo treatment group were diarrhea and headache, reported in 3 (50%) subjects and 2 (33.3%) subjects, respectively. All AEs in the placebo treatment group were considered to be of mild severity.

The most commonly reported AE in subjects in the 80 mg LX6171 treatment group was headache, reported in 2 (33.3%) subjects. The majority of AEs in the 80 mg LX6171 treatment group were considered to be of mild severity. Subject [redacted] had a blood creatine phosphokinase increased that was considered to be severe and AST increased

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that was considered to be of moderate severity. Subject [redacted] had rhinitis that was considered to be of moderate severity and Subject [redacted] had influenza like illness that was considered to be of moderate severity.
No AE was reported in more than one subject in the 160 mg LX6171 treatment group and all AEs were considered to be of mild severity.
The most commonly reported IMP-related AE in subjects in the placebo treatment group was diarrhea, reported in 2 (33.3%) subjects. The most commonly reported IMP-related AE in subjects in the 80 mg LX6171 treatment group was headache, reported in 2 (33.3%) subjects. No IMP-related AE was reported in more than one subject in the 160 mg LX6171 treatment group.
There were no notable median changes from baseline in any hematology or clinical chemistry parameter in the 80 mg LX6171, 160 mg LX6171 or placebo treatment groups. With the exception of the QT interval, there were no notable mean changes from baseline in vital signs or ECG results. There were small median increases and decreases from baseline in the QT interval in all 3 treatment groups at a number of timepoints after the first dose of IMP. There were no changes in physical examination findings during Stage B1 of the study.
Stage B2: No SAEs were reported during Stage B2 of the study, no subject died and no subject was withdrawn as a result of an AE during Stage B2.
For Stage B2, AEs and IMP-related AEs were reported for a higher proportion of subjects in the placebo treatment group (26 [81.3%] subjects for both AEs and IMP-related AEs) than for subjects in either of the LX6171 treatment groups. The lowest proportion of subjects with AEs and IMP-related AEs was seen in the 120 mg LX6171 treatment group (22 [61.1%] subjects and 20 [55.6%] subjects, respectively.
In the placebo treatment group, the most commonly reported AEs were headache (9 [28.1%] subjects), diarrhea (7 [21.9%] subjects), and abdominal pain (5 [15.6%] subjects). The majority of AEs in the placebo treatment group were considered to be of mild severity. Three subjects in the placebo treatment group experienced AEs of moderate severity: Subject [redacted] (diarrhea and nausea), Subject [redacted] (syncope), and Subject [redacted] (soft tissue injury).
In the 120 mg LX6171 treatment group, the most commonly reported AEs were dizziness and headache, each reported in 5 (13.9%) subjects. The majority of AEs in the 120 mg LX6171 treatment group were considered to be of mild severity. Six subjects in the 120 mg LX6171 treatment group experienced AEs considered to be of moderate severity: Subject [redacted] (pain in extremity), Subject [redacted] (muscle spasms), Subject [redacted] (flatulence), Subject [redacted] (cystitis), Subject [redacted] (dizziness), and Subject [redacted] (toothache).
In the 240 mg LX6171 treatment group, the most commonly reported AE was headache, in 10 (28.6%) subjects. Dizziness and insomnia were each reported in 5 (14.3%) subjects dosed with 240 mg LX6171. The majority of AEs in the

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240 mg LX6171 treatment group were considered to be of mild severity. Two subjects in the 240 mg LX6171 treatment group experienced AEs considered to be of moderate severity (headache and back pain). One subject in the 240 mg LX6171 treatment group had an AE of insomnia with a missing severity, and therefore severity for this AE was set to severe.

In Stage B2, headache was the most commonly reported IMP-related AE in all 3 treatment groups, reported for 9 (28%) subjects in the placebo treatment group, 5 (13.9%) subjects in the 120 mg LX6171 treatment group, and 10 (28.6%) subjects in the 240 mg LX6171 treatment group.

Other commonly reported IMP-related AEs in the placebo treatment group were diarrhea (7 [21.9%] subjects), and abdominal pain (5 [15.6%] subjects). Other commonly reported IMP-related AEs in the 120 mg LX6171 treatment group were dizziness (5 [13.9%] subjects), fatigue and somnolence, each reported in 3 (8.3%) subjects . Other commonly reported IMP-related AEs in the 240 mg LX6171 treatment group were dizziness (5 [14.3%] subjects), insomnia (5 [14.3%] subjects), and abdominal pain, diarrhea, and nausea each reported in 3 (8.6%) subjects.

There were no notable median changes from baseline in any hematology or clinical chemistry parameter in the 120 mg LX6171, 240 mg LX6171 or placebo treatment groups. With the exception of the QT interval, there were no notable mean changes from baseline in vital signs or ECG results. There were small median decrease from baseline in the QT interval in 120 mg LX6171 treatment group. One subject in the placebo treatment group had a cardiovascular abnormality of systolic heart murmur on physical examination at the Screening Visit which was normal at baseline (Day -1). The systolic murmur was present at Day 28 and therefore described as changed from baseline. There were no other changes in the abnormalities recorded for the remaining subjects during Stage B2 of the study..

Stages B1 and B2 combined: No SAEs were reported and no subject died during Stages B1 and B2 combined. One subject (80 mg LX6171, Stage B1) was withdrawn from the study because of AEs of AST increased and blood creatine phosphokinase increased.

For Stages B1 and B2 combined AEs and IMP-related AEs were reported for a higher proportion of subjects in the placebo treatment group (32 [84.2%] subjects and 31 [81.6%] subjects, respectively) for both AEs and IMP-related AEs) than for subjects in either the low dose (80 and 120 mg LX6171) or high dose (160 and 240 mg LX6171) LX6171 treatment groups. There was little difference in the proportion of subjects with AEs and IMP-related AEs between the low dose LX6171 treatment group and the high dose LX6171 treatment group.

For Stages B1 and B2 combined, the most commonly reported AE and IMP-related in all 3 treatment groups was headache. The majority of IMP-related AEs in all treatment groups were considered to be possibly related to the IMP and were of mild severity.

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Conclusion:

Stage A: In Stage A of the study, the estimate of relative bioavailability for the 40 mg/mL formulation relative to the 80 mg/mL formulation was 86.7% and 105.3% for LX6171 and LP-523122, respectively.

Estimates of relative bioavailability of LX6171 for the 40 mg/mL and 80 mg/mL formulations dosed in this study compared to the suspension dosed in the previous Phase 1b study (LX6171.1-102-NRM) were 124.9% and 144.0%, respectively.

Estimates of relative bioavailability of LP-523122 for the 40 mg/mL and 80 mg/mL formulations dosed in this study compared to the suspension dosed in the previous Phase 1b study (LX6171.1-102-NRM) were 251.5% and 238.8%, respectively.

Review of predose LX6171 and LP-523122 trough concentrations from Days -1, 7, 14, 21, 28 and 35 confirmed that steady state was reached by Day 21 or Day 28 in all subjects for both LX6171 and LP-523122.

In Stage A of the study, the highest mean plasma concentration of LX6171 was seen at 3 h after dosing in the 40 mg/mL LX6171 treatment group and at 4 h after dosing in the 80 mg/mL LX6171 treatment group. The highest mean plasma concentration of LP-523122 was seen at 3 h after dosing in both the 40 mg/mL LX6171 and 80 mg/mL LX6171 treatment groups.

LX6171 300 mg was considered to be safe and well tolerated at concentrations of 40 mg/mL and 80 mg/mL when administered as a single dose oral suspension to healthy elderly subjects in Stage A of the study.

Stage B: LX6171 at doses of 80 mg, 120 mg, 160 mg and 240 mg administered as an oral suspension once daily for 28 days to subjects exhibiting AAMI was considered to be safe and well tolerated in Stage B of the study.

CDR results showed that there was little evidence from the study to support the hypothesis that LX6171 improved cognition in healthy elderly volunteers exhibiting AAMI, when the compound was administered as daily oral doses over 28 days, in the dose range of 80 mg to 240 mg.

Statistical analysis of MAC-S total scores for the combined Stage B1 and B2 treatment groups showed that the placebo-treated group had a statistically significant improvement with respect to subjects' ability to remember as measured by MAC-S total score compared with low dose LX6171. There was no evidence of a statistically significant effect on word recall as measured by the 15-word recall test (acquisition score or short term delayed recall scores) for any LX6171 or placebo treatment group.

In Stage B1 of the study, the highest mean trough plasma concentration of LX6171 was seen at Day 28 in both the 80 mg LX6171 and 120 mg LX6171 treatment groups. The highest mean trough plasma concentration of metabolite, LP-523122, was seen at Day 21 and Day 28 in the 80 mg LX6171 treatment group and at Day 28 in the 120 mg LX6171 treatment group. In Stage B2 of the study, the highest trough plasma concentrations of LX6171 and the metabolite, LP-523122 were seen at Day 28 in both

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the 120 mg LX6171 and 240 mg LX6171 treatment groups.	