These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

Proprietary Drug Name:	**Generic Drug Name:**	**Therapeutic area and FDA approved indications:**
Vyvanse®	Lisdexamfetamine dimesylate (LDX)	Vyvanse is indicated for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD)

Name of Sponsor/Company:

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Title of Study:

A Long-Term, Open-Label, and Single-Arm Study of NRP104 30mg, 50mg, or 70mg per Day in Adults with Attention Deficit Hyperactivity Disorder (ADHD)

Study Center(s):

Multi-center study with a total of 44 sites.

Studied period:	**Phase of Development:**
05-July-06 to 16-November-07	III

Objectives:

The primary objective of this study was to assess the long-term safety and tolerability of three NRP104 doses of 30mg, 50mg and 70mg, administered at the same time daily, in the treatment of adults with ADHD.

Secondary objectives were:

- To assess the long-term efficacy of NRP104 on symptoms of ADHD by comparing the changes in ADHD-rating scale (ADHD-RS) (assessed using adult Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; Text Revision (DSM-IV-TR™) prompts), from baseline over the course of treatment.
- To assess the long-term improvement with the treatment of NRP104 using the global impressions of ADHD severity and improvement from the clinician (Clinical Global Impression Scale for Improvement [CGI-I])
- To assess the impact of NRP104 on parameters of sleep by self-report of the Pittsburgh Sleep Quality Index (PSQI).

Methodology:

This was a multi-center, open-label, and single-arm study to assess the safety of three NRP104 (herein referred to as LDX) doses (30, 50, or 70mg per day) for up to 1 year in the treatment of adults with ADHD. Subjects who met all inclusion/exclusion criteria, were randomized, and completed at least 2 weeks of study participation in study NRP104.303 were eligible for participation in this study. The study consisted of three periods: a screening/baseline period, a 4-week dose titration, and a long-term maintenance of up to 11 months.

Dose Titration

All subjects initiated treatment at a dose of LDX 30mg for the first week. At the subsequent four weekly visits (Visits 2, 3, 4, and 5), the subject's daily dose of LDX could be increased or decreased by 20mg at weekly intervals to achieve the optimal efficacy and tolerability, if deemed appropriate by the investigator. In this study, the maximum daily dose of LDX that could be received by the subject was 70mg, and the minimum daily dose of LDX the subject must take to continue the treatment was 30mg.

Monthly Maintenance

At the end of the initial 4-week dose titration (Visit 5), subjects entered the long-term maintenance period of up to 11 months. Monthly visits, starting with Visit 6, had a window of ±4 days. All visits were scheduled relative to the $baseline_{304}$ visit date. The last scheduled visit of the study was Visit 16 at Month 12. During the long-term maintenance period, the subject's dose could be increased or decreased by 20mg at any visit, if deemed appropriate by the investigator, to maintain optimal treatment in terms of efficacy and tolerability. All reasons for dose changes were documented by the investigator during the maintenance period. Subjects who could not maintain the minimum daily dose of LDX 30mg due to intolerance were withdrawn from the study.

Safety and Efficacy Assessments

The baseline ADHD-RS, CGI-S, and PSQI scores from study NRP104.303 were utilized as the baseline scores for this study. The ADHD-RS performed using adult ADHD-RS with prompts and the Clinical Global Impression (CGI) were assessed at each post-$baseline_{304}$ visit (Visits 2 to 16) by the investigator. The PSQI was assessed once every 3 months following baseline.

Adverse events (AEs) and concomitant medications were recorded at each visit starting from the baseline visit. Vital signs were measured at each visit beginning with the screening visit. Physical exam and clinical laboratory tests (including pregnancy tests) were assessed at screening, Visit 10 and the final visit. Weight was measured at screening, baseline, and every month thereafter. Height was measured at the screening visit and final visit. Electrocardiogram (ECG) parameters were measured at screening, baseline, and every 3 months thereafter.

Number of Patients (planned and analyzed):

The protocol planned for approximately 300 subjects to be enrolled into the study to result in approximately 100 subjects with 12 months of drug exposure in NRP104-304.

Diagnosis and Main Criteria for Inclusion:

Subjects were 18-55 years, had satisfied DSM-IV-TR™ criteria diagnosis of ADHD, combined, inattentive, or hyperactive-impulsive subtypes, and had completed at least two weeks of study participation in study NRP104.303.

Test Product, Dose and Mode of Administration:

Sponsor provided the LDX capsules of 30mg, 50mg, and 70 mg for oral administration. Capsules were taken orally once each day in the morning.

Duration of Treatment:

The treatment duration in this study is up to 1 year for an individual subject.

Reference Therapy, Dose and Mode of Administration:

None Applicable

Criteria for Evaluation:

Efficacy:

The primary efficacy measure of the study is the investigator-administered ADHD-RS assessed using adult DSM-IV-TR™ prompts for each subject at each study visit after baseline. The ADHD-RS assessed on the last treatment visit is defined as the treatment endpoint for primary efficacy evaluation. The baseline ADHD-RS assessment obtained in study NRP104.303 was transferred into this study and utilized as the baseline assessment. The ADHD-RS consists of 18 items designed to reflect current symptomatology of ADHD. Each item is scored on a 4-point scale ranging from 0 (no symptoms) to 3 (severe symptoms), with the total score for the rating scale ranging from 0-54. The adult DSM-IV prompts were used when administering the scale in order to ensure thorough responses by subjects.

The secondary efficacy measure was Clinical Global Impression of Improvement (CGI-I). The baseline CGI-S of Severity (CGI-S) obtained in study NRP104.303 was used as the baseline severity for this study. At each study visit after baseline, the investigator assesses the subject's improvement relative to the symptoms at baseline on the CGI-I, an 7-point scale ranging from 1 (very much improved) to 7 (very much worse) and included a not assessed option (0). Ratings were completed with respect to ADHD symptoms.

Safety:

Adverse events, vital signs, laboratory parameters, ECG measurements, physical examination, and weight as well as PSQI were utilized to evaluate the safety and tolerability of LDX compared to placebo.

The PSQI is a self-rated questionnaire designed to assess sleep quality and disturbances. Eighteen individual items generate a global score (0-21, where a higher number reflects worse sleep quality) summarized from seven component scores including: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Statistical Methods:

Primary efficacy analysis

The primary efficacy analysis is mean change in the ADHD-RS score from baseline to endpoint, using a paired t-test for each post-baseline visit, for the ITT population. The ITT population included all of the treated subjects who had a baseline assessment and at least one post-baseline primary efficacy assessment. The treatment endpoint is defined as the last post-baseline treatment visit for which a valid ADHD-RS score has been obtained.

Secondary efficacy analysis

CGI-I scores have been dichotomized and reported descriptively for treatment endpoint and for each post-baseline visit.

Safety analysis

Incidence of subjects reporting TEAEs have been reported for each 8-week period and for the entire treatment period, for each of the three NRP104 doses administered. Vital signs, ECG parameters, laboratory tests, and PSQI scores were analyzed to assess the change in a parameter from baseline over the course of the study.

SUMMARY RESULTS:

Subject demographics and baseline characteristics:

A total of 349 subjects were enrolled in this study. The majority of the safety population was Caucasian (82.5%). Slightly more than half were male (54.4%). The majority of subjects was less than 50 years old at study entry and evenly distributed among the age groups 18-29 (31.8%), 30-39 (28.9%), and 40-49 (28.7%). The mean age, weight, and height was 35.8 years, 174.9 pounds, and 67.6 inches, respectively, at study entry. More than 96% of the subjects enrolled from study NRP104.303 within 7 days of the exit visit of that study. Baseline characteristics were comparable across the groups (with and without active preceding treatment).

Efficacy results:

The results of this long-term, open-label study demonstrate the efficacy of LDX at doses of 30 to 70mg per day is maintained through 12 months of treatment without evidence of tolerance. For subjects in the ITT Population, AHDH-RS total scores were statistically significantly decreased from baseline of the antecedent protocol to endpoint ($p<0.0001$) by a mean (standard deviation [SD]) of -24.8 (11.7), which was a greater than 60% improvement over baseline ($baseline_{303}$ score of 40.6 and an endpoint score of 15.8). Significant ($p<0.0001$) changes from $baseline_{303}$ were observed at each post-$baseline_{304}$ visit and were maintained through endpoint. The pattern of changes from $baseline_{303}$ was similar for those subjects with and without active preceding treatment.

Sustained efficacy of LDX was further supported by the results from the results of the CGI-I. Overall, 84.1% of subjects, 79.6% who had received placebo and 84.8% who received LDX in the preceding study, were considered Improved from baseline of the antecedent protocol on the CGI-I at endpoint.

Safety:

In the safety population (N=349), subjects were exposed to LDX for a mean (SD) of 266.4 (124.0) days. A total of 261 (74.8%) subjects were exposed to LDX for 6 months or more (defined as the length of exposure ≥25 weeks), and 195 subjects (55.9%) were exposed to LDX for 49 weeks or longer. The most frequently prescribed daily dose was 70mg (the highest dosage).

Of the subjects enrolled, 191 (54.7%) completed the study, and 158 (45.3%) discontinued study drug. Of these, 28 (8.0%) discontinued due to AEs; 11 (3.2%) discontinued for lack of efficacy; 27 (7.7%) discontinued due to protocol violation; 41 (11.7%) were lost-to-follow-up; 42 (12.0%) withdrew consent; 1 (0.3%) was discontinued at the investigator's discretion; and 7 (2.0%) discontinued for other reasons.

Overall, 87.7% of subjects experienced at least one AE during the study. The incidence of subjects experiencing an AE was similar between subjects who had received LDX in the previous study (88.2%) and those who had received placebo (84.6%). However, the incidence of possibly or probably related AEs was lower in subjects who received LDX in the previous study (68.7%) compared with subjects who received placebo (78.8%). This finding may be related to the fact that subjects who were randomized to placebo in the previous study first encountered LDX in this study. Approximately 70% of the AEs were judged by the investigator as either possibly or probably related to study medication. The incidence of severe AEs was similar between subjects who had received LDX in the previous study (12.1%) compared with subjects who had received placebo (11.5%). Nearly 75% of the TEAEs occurred within the initial 8 weeks of treatment.

Eight (2.3%) subjects experienced a total of ten serious AEs (SAEs); all were judged by the investigator to be unrelated to study drug. The ten SAEs occurred in subjects who were randomized to active treatment in the antecedent study.

One subject died from cocaine and alcohol toxicity unrelated to study drug.

The TEAEs experienced by >5% subjects in the safety population were upper respiratory tract infection (21.8%), insomnia (19.5%), headache (17.2%), dry mouth (16.6%), decreased appetite (14.3%), irritability (11.2%), anxiety (8.3%), nasopharyngitis (7.4%), sinusitis (6.6%), weight decreased (6.0%), back pain (5.4%), and muscle spasms (5.2%).

Of the 1673 TEAEs experienced post-baseline by subjects in the study, 1027 events in 263 (75.4%) subjects were mild in severity, 590 events in 222 (63.6%) subjects were moderate, and 56 events in 42 (12.0%) subjects were severe. There were 12 severe TEAEs in ten (2.9%) subjects that were considered possibly or probably related to treatment.

A total of 28 (8.0%) subjects discontinued because of TEAEs: five (1.4%) while taking LDX 30mg per day; ten (3.1%) while taking 50mg per day; and 15 (6.3%) while taking 70mg per day. The TEAEs associated with study discontinuation that occurred two or more times in the safety population were insomnia (three events); and anxiety, dizziness, and dysphoria (two events each). Three additional subjects were withdrawn because of a positive pregnancy test.

The mean changes in blood pressure (BP) and pulse rate from baseline to the endpoint and to the post-baseline$_{304}$ visits were generally small in magnitude and consistent with known effect of stimulants.

There were no ECG records with a QTcF (Fridericia) interval of >480msec across any of the treatment visits or at baseline. One subject had a clinically significant abnormal QT prolongation (QT interval 405msec, QTcB 511msec, QTcF 473msec) at Month 6. However, a supplemental ECG reading 11 days later revealed that the values had returned to normal (407, 441, 429msec, respectively). Overall, the mean changes from baseline for heart rate and QT/QTc intervals were small and not clinically relevant, ranging from 3.4 to 4.9bpm for heart rate, -5.9 to -0.4msec for QT, 2.4 to 7.7msec for QTcF, and 6.8 to 12.1msec for QTcB. There was no apparent pattern over time with respect to heart rate or the QTcF or QTcB interval changes from baseline.

The average decrease in body weight from baseline$_{304}$ to endpoint was 4.0lb, which was approximately a 2% reduction relative to the safety population mean value at baseline$_{304}$. With the exception of Months 11 and 12, mean change from baseline$_{304}$ in body weight was increasingly negative with time on treatment and ranged from a mean loss of 2.6 (8.1) pounds at Week 4 to a mean loss of 6.8 (11.4) pounds at Month 10.

Mean changes in laboratory values and findings of physical examinations were not clinically meaningful and no trends were apparent in the changes that were noted.

Overall mean (SD) changes in sleep quality from baseline to endpoint as measured by the PSQI were -1.3 (2.8), which demonstrates that overall sleep quality was not meaningfully changed while subjects were treated with LDX.

OVERALL SUMMARY:

LDX (30, 50, and 70mg) was well tolerated and provided continued efficacy in adults with ADHD who completed up to 12 months of treatment with LDX.