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Prescribing decisions should be made based on the approved package insert.*

Proprietary Drug Name:

Vyvanse™

Generic Drug Name:

Lisdexamfetamine Dimesylate
(NRP104)

Therapeutic area and FDA approved indications:

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children aged 6 to 12.

Name of Sponsor/Company:

Shire, Inc.

Title of Study:

A Phase 2, Randomized, Double-Blind, Placebo- and Active-Controlled, 3-Treatment, 3-Period, Crossover Study with One Week Per Treatment and Once-a-Day Dosing of Either NRP104, Adderall XR®, or Placebo in Children Aged 6 to 12 Years with Attention-Deficit Hyperactivity Disorder (ADHD)

Study Center(s):

Multi-center study

Studied period:

First enrollment date: September 30, 2004
Last completion date: December 23, 2004

Phase of Development: II

Objectives:

Primary

The primary objective of this study was to assess, in a controlled environment, the efficacy and safety of NRP104 and Adderall XR, compared to placebo in treatment of children (aged 6-12) with ADHD as defined by Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision criteria (DSM-IV-TR). The therapeutic responses were determined using the Swanson, Kotkin, Agler, M. Flynn and Pelham (SKAMP) and Permanent Product Measure of Performance (PERMP) rating scales measured throughout a treatment assessment day.

Secondary

- To assess the duration of therapeutic responses to NRP104 and Adderall XR compared to placebo.
- The duration of therapeutic responses were determined using SKAMP and PERMP measured at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post morning dose.
- To evaluate the efficacy of NRP104 and Adderall XR compared to placebo, based on the Clinical Global Impression (CGI).
- To evaluate the safety of NRP104 based on occurrence of treatment-emergent adverse events and specific evaluation of blood pressure, and heart rate.
- To evaluate PK profile and PK/PD relationship of NRP104 after multiple doses.

Methodology:

This was a Phase 2, randomized, multi-center, double-blind, 3-treatment and 3-period crossover study conducted in a school laboratory environment to evaluate efficacy and safety of NRP104 (30 mg, 50 mg, or 70 mg) and Adderall XR (1x10 mg, 2x10 mg, or 3x10 mg) compared with placebo in treatment of children with ADHD. The school laboratory environment included an analog classroom and lasted for a 13-hour school day. The entire study consisted of three periods and one final study visit.

Screening Period (Visit 1): 1 week, during which subjects were screened for study participation. Eligible subjects were those aged 6 to 12 years who were treated with a stimulant drug for at least one month in the last six months for ADHD.

Dose Titration Period (Visits 2 to 5): a 3-week open-label dose titration with Adderall XR (Visits 2 to 4) and a practice assessment day (Visit 5). Subjects meeting inclusion/exclusion criteria returned to the clinic at the enrollment visit (Visit 2) for collection of baseline measures and evaluation of continued eligibility. Eligible subjects entered the dose titration period, during which they received Adderall XR for the treatment of ADHD in an open-label fashion. Subjects started the dose titration with 10 mg per day of Adderall XR for the first week. At the next weekly visit (Visit 3), the investigator evaluated, based on the CGI, interview with the parents, and safety data, the subject's therapeutic responses and tolerability to treatment and decided whether the current Adderall XR dose should be increased or remain the same for the second week of titration. If the decision was to increase the dose, the subject would receive 20 mg per day of Adderall XR in the next titration week. At the subsequent weekly visit (Visit 4), the investigator evaluated the subject again and decided whether the current dose should be increased or decreased or remain the same. If the decision was to increase the dose, the daily dose would be increased by 10 mg Adderall XR in the next titration week for this subject. If the decision was to decrease the dose, the subject would receive 10 mg per day of Adderall XR in the next titration week.

The Adderall XR dose determined at the end of the titration period was considered as the optimal dose in this study. The optimal dose identified for each subject was used for the subsequent double-blind period for the treatment of ADHD. On the last day of the dose titration period (Visit 5), a practice assessment day was conducted in the laboratory school environment. Subjects came to the laboratory school location for a group orientation and practice day that served to familiarize them with the staff and procedures associated with double-blind visits 6 to 8. Subject randomization and double-blind treatment distribution occurred at the end of this visit. The treatment allocation ratio was 1:1:1.

Double-Blind Crossover Period (Visits 6 to 8): a 3-way crossover treatment of one week each during which the subject received either NRP104, Adderall XR, or placebo in a double-blind and randomized fashion. Subjects who were randomized at the end of the practice visit (Visit 5) to receive the double-blind treatment were provided with the randomized medication product for the 1st double-blind treatment week at the end of the practice visit. The three treatments each randomized subject received during the 3-week double-blind period were determined by the optimal Adderall XR dose obtained for him/her at the end of the dose titration period using the following conversion table:

Optimal Adderall XR Dose Obtained At the end of Dose Titration Period	Treatment Dose to Receive in Double-Blind Crossover Period
Adderall XR 10 mg/day	NRP104 30 mg/day or Adderall XR 10 mg/day (1x10 mg) or Placebo
Adderall XR 20 mg/day	NRP104 50 mg/day or Adderall XR 20 mg/day (2x10 mg) or Placebo
Adderall XR 30 mg/day	NRP104 70 mg/day or Adderall XR 30 mg/day (3x10 mg) or Placebo

During each double-blind week, subjects took the treatment dose each morning at home for the first 6 days, and the Day 7 dose of the treatment was administered at the laboratory school visit. Subjects returned on Day 7 of each double-blind week for a laboratory school assessment.

During each laboratory school assessment day (including the practice visit), classroom sessions were arranged at approximately 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post morning dose, and each classroom session lasted for about 30 minutes. Efficacy measures of the SKAMP and PERMP were collected during each of the 8 sessions. During the double-blind period, the CGI was assessed at the laboratory school visit for that treatment week.

At the end of the 7th day of the first and second double-blind weeks (i.e., Visits 6 and 7), subjects received blinded treatment supplies for the following week.

During the last laboratory school assessment day (Visit 8), blood samples were taken to assess plasma levels of NRP104 (*d*-amphetamine and intact NRP104) and Adderall XR® (*d*-amphetamine and

-amphetamine) for all subjects at pre-dose (0 hour) and at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post dose.

Final Study Visit (Visit 9): All subjects who received study medication including the open-label Adderall XR were seen for a final study visit (or end of study visit) for safety evaluation. The final study visit occurred within three (3) days following the last laboratory school visit or at the time of early study withdrawal.

Throughout the study, a total of 9 visits were scheduled: Visit 1 (Screening), Visit 2 (Enrollment), Visits 3-4 (Titration), Visit 5 (Practice/Randomization), and Visits 6-8 (Double-Blind Crossover), as well as Visit 9 (Final Study Visit/End of Study Visit). Visits 5-8 were conducted at the laboratory school facility. The subject provided a medical history and underwent a physical examination at the screening visit. Physical examination was also performed at the final study visit (Visit 9). Blood and urine samples for routine clinical laboratory analysis and pregnancy testing were collected during the screening visit and final study visit. Vital signs were measured at screening visit, enrollment visit, titration visits, and final study visit, as well as periodically throughout the laboratory school day. ECG was collected at screening visit and final visit as well as periodically throughout the laboratory school day. Adverse events and concomitant medications were recorded at each study visit.

Additionally, the subject was followed up with a telephone call approximately 30 days following the discontinuation of the study medication to collect any serious adverse events that may have occurred to the subject during that period.

Number of Patients (planned and analyzed):

The primary efficacy parameter in this study is the SKAMP Department Scale (SKAMP-DS). Previous studies of amphetamines in treatment of children with ADHD disclosed an effect size of greater than 0.50. Assuming the same effect size for NRP104, it required to complete approximately 40 subjects in this crossover study for a power of greater than 0.80 to detect a difference between NRP104 and placebo at the significance level of 0.05 (2-sided) using a related t-test. Using a balanced 3x3 Latin-Square with 6 treatment sequences, this study planned to randomize 48 subjects.

Fifty-two (52) subjects enrolled into the study and received the open-label treatment. All of them were randomized with 50 subjects completing the study. The intention-to-treat population of 50 subjects was analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:

Subjects were 6 to 12 years, had satisfied DSM-IV-TR criteria diagnosis of ADHD, combined or hyperactive-impulsive subtypes, and were on a stable regimen of stimulants for at least one month in the last six months and showed adequate response to stimulants without unacceptable side effects.

Test Product, Dose and Mode of Administration:

Sponsor provided the NRP104 capsules of 30 mg, 50 mg, and 70 mg for oral administration. Capsules were taken orally once each day in the morning.

Duration of Treatment:

Prior to being randomized to the double-blind treatment, subjects were titrated with Adderall XR in an open-label fashion for 3 weeks. During the double-blind phase, subjects received daily study medication for one week with each of the three treatments (i.e., NRP104, Adderall XR, and placebo). Thus, the total treatment duration was six weeks for a subject.

Reference Therapy, Dose and Mode of Administration:

The sponsor provided Adderall XR 10 mg in capsules and matching placebo capsules given orally once each day in the morning. Adderall XR 10 mg capsules were also used in the open-label dose titration phase.

Criteria for Evaluation:**Efficacy**

The primary efficacy measure of the study is the SKAMP Department Scale (SKAMP-DS) (Wigal et al., 1998). The average of the SKAMP-DS scores across a treatment assessment day during the randomized treatment period was defined as the primary efficacy endpoint. SKAMP-DS was measured at 1, 2, 3, 4.5, 6, 8, 10, and 12 hours post the morning dose on the treatment assessment day for a total of eight times, which were utilized to assess the duration of therapeutic responses of NRP104 as compared to placebo and Adderall XR.

Secondary efficacy measures of this study include:

SKAMP Attention Scale (SKAMP-AS) (Wigal et al., 1998), which was collected at the same time as the SKAMP-DS. PERMP Derived Measures, which was measured at the same time as the SKAMP. The PERMP consists of two measures: PERMP attempted score (PERMP-AS) and PERMP correct score (PERMP-CS).

Clinical Global Impression (CGI), including Severity (CGI-S) at baseline, and Improvement (CGI-I) at subsequent visits, Visit 2 through Visit 8, was collected.

PK Parameters

PK parameters included AUC(0-t), C_{max}, and T_{max} based on the blood samples collected on the last laboratory school assessment day (Visit 8) as well as the plasma drug concentration at each time point collected.

Safety

Treatment-emergent adverse events, vital signs, laboratory parameters, and ECG measurements as well as physical examination were utilized to evaluate the safety and tolerability of NRP104 compared to placebo and Adderall XR.

Statistical Methods:

Primary efficacy analysis

The primary efficacy analysis was conducted on the primary efficacy endpoint (i.e., the average of SKAMP-DS across the treatment assessment day), using a mixed-effects model of analysis of variance (ANOVA) for the intention-to-treat (ITT) population. The ITT population was defined as all of the randomized subjects who had at least one SKAMP-DS treatment average score post randomization. The model utilized SAS PROC MIXED to perform this analysis and included treatment (3 levels) and period (3 levels) as fixed effects, and subject-within-site as random effect. The 3 treatment levels were NRP104 (30 mg, 50 mg, and 70 mg combined), Adderall XR (10 mg, 20 mg, and 30 mg combined), and placebo.

Given a significant overall treatment effect ($p < 0.05$), pairwise comparisons of least-square means between individual treatments were further conducted using a t-test. The primary efficacy pairwise comparison in this study was NRP104 (30 mg, 50 mg, and 70 mg combined) vs. placebo, and the p value for this comparison was tested at the significance level of 0.05. In addition, pairwise comparisons were tested between Adderall XR (10 mg, 20 mg, and 30 mg combined) vs. placebo and between NRP104 vs. Adderall XR and reported.

Sub-group analyses by each optimal dose cohort were performed on the primary efficacy endpoint to evaluate dose-response relationship.

Secondary efficacy analysis

The same mixed-effects model and analytical approach described above was used to evaluate, respectively, the SKAMP-AS, PERMP-AS, and PERMP-CS averages across the treatment assessment day as well as the CGI-I.

To evaluate the duration of the therapeutic responses, the SKAMP and PERMP measures observed at each classroom session of the treatment assessment day were analyzed using the same mixed-effects model followed by a t-test pairwise comparison of an active treatment vs. placebo. The hypothesis of duration of therapeutic responses of an active treatment vs. placebo was tested using a closed testing procedure at the p value of 0.05 level. The closed testing procedure started from the time point of 1 hour post-morning dose, then 2 hours, 3 hours, 4.5 hours, 6 hours, 8 hours, 10 hours, and 12 hours post dose. The onset time of the effect was determined at the time point when the difference between the two treatments (active vs placebo) first became significant. The duration of efficacy action was claimed at the last time point beyond which the level of significance exceeded 0.05.

Sub-group analyses by each optimal dose cohort were performed on each time point to evaluate assay sensitivity of the duration of efficacy action.

PK/PD analysis

PK/PD correlation of *d*-amphetamine with SKAMP and PERMP measures were assessed, using Pearson correlation coefficient, for both NRP104 and Adderall XR.

Safety analysis

Safety parameters were analyzed to compare the difference among the treatment groups. Parameters included treatment-emergent adverse events, vital signs, and ECG measurements. Outlier analyses were also performed based on the study-defined cut-off values of a vital sign or ECG parameter.

SUMMARY RESULTS

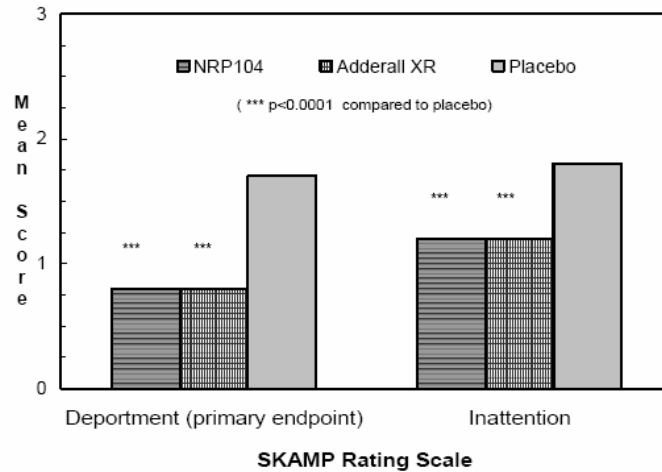
EFFICACY:

Over 80% of subjects aged 6 to 12 years with ADHD in this study required Adderall XR daily doses of 20 mg or higher to control the ADHD symptoms and behaviors. The mixed-effects model resulted in a highly significant treatment effect ($p < 0.0001$) on the primary efficacy endpoint, the SKAMP Department average across the 8 sessions observed under the treatment assessment day, and on all secondary efficacy endpoints. Pairwise comparisons of NRP104 vs. placebo and Adderall XR vs. placebo indicated that for either the primary or secondary efficacy endpoints, significant improvements were seen in favor of the NRP104 ($p < 0.0001$) and Adderall XR ($p < 0.0001$). There were no apparent differences in efficacy between NRP104 and Adderall XR. The results of the primary efficacy analysis are provided in both tabulation (Table A) and graphics (Figure A) below.

Parameter	NRP104	Adderall XR	Placebo
N (ITT=50)	50	50	50
Mean (SD)	0.8 (0.7)	0.8 (0.8)	1.7 (1.2)
LS Mean (SE)	0.8 (0.1)	0.8 (0.1)	1.7 (0.1)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-0.9 (-1.1, -0.7)****
Difference in LS Mean (95% CI) of Adderall XR vs. Placebo			-0.9 (-1.1, -0.7)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR		-0.1 (-0.3, 0.1)	

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ (2-way ANOVA with treatment and period effects)
Source: Section 15 Table 2.1.1

Figure A
SKAMP LS Mean Across Assessment Day: ITT Population



SUMMARY RESULTS (continued)

The investigators rated on the CGI, respectively, 74% and 72% of subjects on NRP104 and Adderall XR as either 'very much improved' or 'much improved,' as compared to 18% of subjects on placebo. Substituting a subject's medication of ADHD treatment from either Adderall XR 10 mg to NRP104 30 mg, or Adderall XR 20 mg to NRP104 50 mg, or Adderall XR 30 mg to NRP104 70 mg, resulted in comparable efficacy effects on the subject's ADHD symptoms and behaviors. When comparing the results among the different optimal dose cohorts, the obtained SKAMP Department means appeared similar among the active treatments of these dose cohorts, but markedly different among the placebo treatments. The magnitude of deteriorations in ADHD symptoms and behaviors under the placebo treatments was evident when compared to the optimal active treatment dose to which the subject was titrated in the open-label period.

SKAMP Department least-square (LS) means revealed a highly significant treatment effect ($p < 0.0001$) at each individual session starting from 2 hours post dose throughout 12 hours post dose. Pairwise comparisons ($p < 0.0001$) were favorable to both active treatments over the course from 2 hours to 12 hours time points, which thus demonstrated that on average, the onset of drug effect was within 2 hours for both NRP104 and Adderall XR, and the therapeutic effect continued throughout the entire assessment time period, that is, 12 hours post morning dose, yielding effectively at least a 12-hour duration of therapeutic responses from dosing time in the morning. Similar results were also obtained for the other secondary efficacy measures.

Consistent with previous findings of amphetamine products, this study observed a moderate relationship between plasma *d*-amphetamine levels and pharmacodynamic measures of SKAMP and PERMP for both NRP104 and Adderall XR.

SAFETY:

A total of 89 treatment-emergent events were reported by 29 (or 56%) of 52 subjects treated in this study. Of those, 52 events occurred during dose titration and 37 during double-blind treatment. Majority of them were mild in severity, and the remaining were moderate. No AEs were severe. The study observed no serious adverse events. One subject was withdrawn in the 1st week of randomized treatment while on placebo due to adverse event (gastroenteritis viral).

In the open-label dose titration, the treatment-emergent AEs with the highest subject incidences included headache (15%), decreased appetite (14%), and insomnia (10%). In the double-blind treatment, the treatment emergent AEs with a greater than 2% subject incidence were insomnia (8%), decreased appetite (6%), and anorexia (4%) for the treatment of NRP104; decreased appetite (4%) and abdominal pain upper (4%) for the treatment of Adderall XR; and, vomiting (4%) for the treatment of placebo. All these AEs reported under the active treatments are commonly observed with treatment of amphetamine products.

Vital signs, measured under the three treatments of the double-blind period, showed that from 2.5 to 5 hours post the morning dose, diastolic BP appeared to have been higher than that of placebo by approximately 5 mmHg and 3 mmHg, respectively, for NRP104 and Adderall XR; and, at 2.5 hours post dose, pulse appeared to have been higher than that of placebo by approximately 7 bpm and 5 bpm, respectively, for NRP104 and Adderall XR. The extent of changes in vital signs under each treatment from baseline was small and no trend was revealed.

ECG parameters, measured under three treatments of the double-blind period, showed that at 5 and 10.5 hours post dose, QT interval appeared to have been greater than that of placebo by approximately 7-14 msec and 5-10 msec, respectively, for NRP104 and Adderall XR; and, at 2.5 and 10.5 hours post dose, QTc (Fridericia) interval appeared to have been greater than that of placebo by approximately 6-8 msec and 5 msec, respectively, for NRP104 and Adderall XR. The extent of changes under each treatment from baseline was small in general in the ECG parameters, and no trend was revealed.

Overall Summary:

NRP104 appears to be an efficacious treatment for childhood ADHD. The onset of effectiveness occurred within 2 hours of dosing. The duration of therapeutic responses of NRP104 and Adderall XR, as compared to placebo, lasted throughout the last time point of the assessment day, demonstrating that this medication provides at least a 12-hour duration of drug action. Direct switch of medication from Adderall XR to NRP104 by substituting Adderall XR 10 mg, 20 mg, and 30 mg, respectively, with NRP104 30 mg, 50 mg, and 70 mg, had resulted in a comparable therapeutic response. Similar to Adderall XR, daily NRP104 doses of 30 mg to 70 mg appear to be well-tolerated.

