CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-977

MEDICAL REVIEW(s)

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for lisdexamfetamine (NRP-104) capsules for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 21-977
[Note: This overview should be filed with the 12-22-06 response to our 12-21-06 approvable letter.]

[Note: See my approvable memos dated 9-28-06 and 12-20-06, Dr. Khin's approval memo dated 2-16-07, and my original 2-21-07 approval memo for background information on this NDA.]

Two other issues were raise------t need to be addressed before final approval, both related to the concerns expressed by Dr. -----/------(see my 2-21-07 memo for my earlier comments on his concerns).

Dr. ----- expressed concern about the relatively small number of patients exposed to lisdexamfetamine in this development program (n=272). Although this is a small number compared to the typical NDA safety database, it is a reasonable number, in my view, given our knowledge that lisdexamfetamine is a prodrug for d-amphetamine, the active substance. We, of course, have substantial information to inform us about the safety profile of d-amphetamine. Furthermore, as I indicated in my 2-21-07 memo, we have substantial information to allow us to conclude that lisdexamfetamine does not have amphetamine-like activity, and, therefore, would not be capable of causing the cardiovascular adverse events that Dr. ----- seems to be concerned about. His concerns are conditioned upon his speculation that there is a subgroup of patients who cannot efficiently cleave lysine from lisdexamfetamine and who, therefore, might have higher levels of lisdexamfetamine than we have generally observed (all the data we have suggests that systemic exposure to lisdexamfetamine is very low following the recommended doses of this prodrug).

The second issue concerns the labeling for this prodrug. ---------- ---------- ---------- ------ ---------- -------- ----------. The best data we have regarding this issue are in vitro data that show that lisdexamfetamine does not bind at the DA and NE reuptake sites that underlie the sympathomimetic effects of amphetamines. Thus, on this basis, lisdexamfetamine would not be expected to have any amphetamine-like activity. As I

have noted in my 2-21-07 memo, in vivo animal data also suggest that lisdexamfetamine does not have amphetamine-like activity. We have added the following statement to labeling: "The parent drug, lisdexamfetamine, does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro." The sponsor has accepted this minor change to the label.

cc:
Orig NDA 21-977
HFD-130
ODE-I/RTemple
HFD-130/TLaughren/MMathis/NKhin/MChuen/FCurtis

DOC: Lisdexamfetamine_Laughren_AP2 Memo.doc

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/s/

Thomas Laughren
2/23/2007 12:32:58 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 21, 2007

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for lisdexamfetamine (NRP-104) capsules for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 21-977
[Note: This overview should be filed with the 12-22-06 response to our 12-21-06 approvable letter.]

[Note: See my approvable memos dated 9-28-06 and 12-20-06 and Dr. Khin's approval memo dated 2-16-07 for background information on this NDA.]

We issued 2 approvable letters for this application (10-6-06 and 12-21-06). The obstacles precluding a final approval action in the last review cycle were predominantly CMC, i.e., there were still concerns about the quality of drug substance coming from the ---- - --- facility, and it was not possible to establish a retest period for drug substance batches or to establish an expiry. These concerns have now been resolved and CMC has recommended an approval action.

There were a few relatively minor clinical labeling issues, and these have also been resolved. In the meantime, we have asked the sponsor to adopt a medication guide that has been developed for other stimulant products, and they have agreed to this. The sponsor has agreed to several minor labeling changes regarding biopharmaceutical issues, and they have agreed to the dissolution specifications proposed by the OCP group. We reached final agreement with the sponsor on labeling and the medguide on 2-16-07.

The sponsor has agreed to a phase 4 commitment to conduct a clinical study in adolescents with ADHD and submit the results within 3 years.

In the draft approval letter we have asked them to make a minor change in the container label to make it easier to read, and we have reminded them that DEA will make a final scheduling determination. We have also reminded them of their commitment not to market this product until scheduling is finalized.

I want to mention for the record one other issue that has been raised during the process of reviewing this new drug. This concern was raised in the form of e-mails to me by a Dr. -----

[redacted], a physician at [redacted]. These e-mails were sent on 10-10-06, 10-31-06, and 2-17-07. I responded to the first e-mail by simply informing Dr. [redacted] that any information pertinent to a pending application was privileged and that I could not discuss any of these matters with him. However, I did share his e-mails with other review staff. His most recent e-mail (2-17-07) was directed to Dr. Von Eschenbach (and copied to me), and in essence, it raises a theoretical concern that there may be a subgroup of children who are unable to cleave L-lysine from the prodrug, lisdexamfetamine, and, they therefore might develop supratherapeutic levels of lisdexamfetamine. Dr. [redacted] suggests that we should have required a very large population to be exposed to this prodrug before approval, presumably to rule out this possibility. He suggests that we might expect "reports of sudden, arrhythmic deaths" once this drug is approved, presumably due to these supratherapeutic levels. My view is that Dr. [redacted] thinking is flawed, since lisdexamfetamine does not, to my knowledge, have any sympathomimetic activity. It is highly speculative to suggest in the first place that there is such a subgroup of patients, but even if there were, it would not be expected that patients having higher than expected levels of lisdexamfetamine would be at risk of sympathomimetic toxicity. I scheduled a meeting with other review staff on 2-20-07 to further discuss this matter, and there was unanimous agreement that there is no basis for Dr. [redacted] expressed concern. The meeting was attended by representatives of CMC (Drs. Oliver, Sood, and Soldatova), pharmacology (Drs. Rosloff and Elayan), OCP (Drs. Baweja and Jackson), and clinical (Dr. Mathis and myself). The following observations were made at this meeting:

-Contrary to Dr. [redacted] assertions, there is remarkably little pharmacokinetic variability with lisdexamfetamine, i.e., an argument against the possibility of genetic variability regarding the cleavage of lysine.

-What genetic variability there is with drug metabolism is seen mostly with oxidative metabolism (i.e., the CYP-450 system), and not with enzymative cleavage which is what underlies the conversion of this prodrug into d-amphetamine. In fact, there are several different enzymes that facilitate this cleavage, which argues against the possibility of genetic differences in any one enzyme resulting in intersubject variability.

-Dr. [redacted] is incorrect in his assertion that it is gastric acid hydrolysis that underlies the lysine cleavage. Rather, as noted, it is enzymatic cleavage that underlies this conversion.

-The other pertinent issue is that Dr. [redacted] is incorrect in his assumption that intact lisdexamfetamine is active. All the available evidence indicates that it is inactive, including both in vitro assays and in vivo animal data. In vitro assays showed that lisdexamfetamine has no activity at DA, NE, and a variety of other receptors. In vivo assays suggest that all the activity of orally administered lisdexamfetamine is due to the d-amphetamine that is released from the prodrug. IV administration of lisdexamfetamine results in increased levels of lisdexamfetamine and decreased levels of d-amphetamine, compared to oral administration of lisdexamfetamine, with a resultant decrease in amphetamine-like activity, because the lisdexamfetamine is without activity. Consequently, Dr. [redacted] expressed concern about toxicity of lisdexamfetamine is completely groundless.

New River Pharmaceuticals, Inc. has, in my view, submitted sufficient data to support the conclusion that NRP1-4 is effective and acceptably safe in the treatment of ADHD. It is my view that all remaining issues have been addressed, including agreement on labeling. Therefore, I recommend that we proceed with a final approval action. Of course, once approved, this

product cannot be marketed until DEA makes a final determination about the controlled substances classification.

cc:
Orig NDA 21-977
HFD-130
ODE-I/RTemple
HFD-130/TLaughren/MMathis/NKhin/MChuen/FCurtis

DOC: Lisdexamfetamine_Laughren_AP Memo.doc

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/s/

Thomas Laughren
2/21/2007 11:39:45 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 16, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-977 (This overview should be filed with the 12-22-2006 submission.)

SUBJECT: Recommendation of Approval Action for Lisdexamfetamine (NRP-104) Capsules for the Treatment of Attention-Deficit Hyperactivity Disorder (ADHD)

1. BACKGROUND

Amphetamine products including dextroamphetamine and mixed salts of a single-entity amphetamine (amphetamine/dextroamphetamine) are available in the U.S. for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). These available stimulant products are known to have a high abuse potential and a possibility of obtaining for non-therapeutic use.

The sponsor's development program of NRP104 is intended for its use in the treatment of ADHD. NRP104 is a pro-drug of d-amphetamine. The active ingredient in NRP104 capsules is lisdexamfetamine dimesylate which lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the GI tract, releasing active d-amphetamine. The proposed commercial formulation of NRP104 is a capsule containing 30 mg, 50 mg or 70 mg of the pro-drug lisdexamfetamine.

The sponsor submitted the above referenced NDA on December 6, 2005. The application included the efficacy results from two clinical studies 201 and 301. We issued an approvable letter on 10/6/06 to which the sponsor responded on 10/24/06. We issued a second approvable letter on 12/21/06 indicating that the sponsor needed to address some CMC issues prior to taking a final action. The sponsor responded to the second approvable letter in a submission dated 12/22/06.

This response to the second approvable letter has been reviewed by Michelle Chuen, M.D., Medical Officer, DPP (review dated 1/25/07), Andre Jackson, Ph.D. the Office of Clinical Pharmacology (OCP) reviewer (review dated 1/31/07) and Lyudm Soldatova, Ph.D., the CMC reviewer (review dated 2/14/07).

2.0 CHEMISTRY

Based on the CMC review by Dr. Soldatova, the sponsor has addressed all CMC concerns and she found the response acceptable. It was noted that the sponsor has agreed to continue testing drug substance for ------ impurities and----------

---------- The 24-month expiration date for all capsule strengths is granted. From the CMC perspective, it was recommended an approval action.

3.0 PHARMACOLOGY

There is no new pharmacology/toxicology information in this submission.

4.0 CLINICAL PHARMACOLOGY

The sponsor has accepted all of the OCP proposed labeling changes. The sponsor has also agreed to the dissolution specification (Q=----- in 15 minutes). I am not aware of any clinical pharmacology issues that would preclude an approval action of this NDA.

5.0 CLINICAL DATA

5.1 Efficacy and Safety Data

There is no new clinical data in this submission. The sponsor has submitted sufficient data to support that NRP104 is effective and reasonably safe in the treatment of ADHD in pediatric population (6-12 yrs of age).

5.2 Controlled Substance Scheduling

Our FDA-CSS staff has recommended that lisdexamfetamine be classified as a Schedule II controlled substance. The DEA will make a final determination of the controlled substance classification. During the 2/16/07 teleconference with the sponsor, we reminded the sponsor that they should not market the drug prior to final scheduling by the DEA and they committed to do so.

6.0 WORLD LITERATURE

The sponsor stated that a literature search was performed by Shire Pharmaceuticals, Inc. There were no findings that would affect conclusions about the safety of NRP104.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, this drug is not approved for any indication in any country at this time.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

There is no DSI inspection related issue during this review cycle.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. In an email dated 2/13/07, the sponsor has responded that the labeling changes are acceptable. Final labeling should be included in the action letter.

On 2/16/07, we had a teleconference with the sponsor to discuss the items in the Medication Guide. We have reached an agreement on the Med Guide as well.

The sponsor will use Vyvanse as the trade name. The DMETS has evaluated this proprietary name and found it acceptable.

10.2 Foreign Labeling

At this time, I am not aware that NRP104 is approved for the treatment of ADHD anywhere else.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that NRP104 is effective and reasonably safe in the treatment of ADHD in pediatric population (6-12 yrs of age). The sponsor has responded adequately to the CMC concerns. We have reached final agreement with the sponsor regarding the labeling and the Medication Guide. I recommend that we issue an approval action letter.

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/s/

Ni Aye Khin
2/16/2007 01:21:59 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #21-977

Sponsor:	New River Pharmaceuticals, Inc.
Drug:	Lisdexamfetamine Dimesylate Capsules
Indication:	Attention Deficit Hyperactivity Disorder
Material Submitted:	Amendment to a Pending Application Response to Reviewer Request Response to Reviewer Request
Correspondence Date:	December 22, 2006; January 22, 2007; January 24, 2007
Date Received:	December 26, 2006; January 22, 2007; January 25, 2007

I. Background

On 12/6/05, the sponsor submitted this NDA for the approval of lisdexamfetamine dimesylate in the treatment of attention deficit hyperactivity disorder.

The Office issued an approvable letter on 10/6/06 to which the sponsor responded in a 10/24/06 submission. The Office issued a second approvable letter on 12/21/06. In summary, this letter indicated that, prior to approval, the sponsor would need to address several points, to include the following clinical issues:

1) world literature update
2) foreign regulatory update/foreign labeling
3) labeling

The 12/22/06 submission contains their responses to the above.

II. Clinical Data

A. World Literature Update

The sponsor stated that a literature search was conducted by Shire Pharmaceuticals, Inc. Global Medical Affairs utilizing the following databases: Medline, Embase, International Pharmaceutical Abstracts, and Biosis. The search terms included "lisdexamfetamine dimesylate,"

"lisdexamfetamine," "lisdexamphetamine," "NRP104," and "NRP 104." Cut-off dates were not provided.

This search yielded five results: two full text articles and three abstracts. The sponsor states that these were systematically, and in detail, and no findings were discovered that would adversely affect conclusions about the safety of NRP104.

B. Foreign Regulatory Update/Foreign Labeling

The sponsor stated that no actions have been taken or are pending before foreign regulatory authorities regarding NRP104. This compound has not been approved by any non-US regulatory body. The sponsor agreed to notify the Agency of all actions by foreign regulatory authorities as requested.

C.   Product Labeling

The following comments are provided regarding the clinical sections of the sponsor's 12/22/06 proposed labeling:
-

-

-

III. Conclusions and Recommendations

This submission is a full and adequate response to the clinical issues raised in our approvable letter.

[1] Per Yeh-Fong Chen, statistical reviewer, via a 12/5/06 email.

From a clinical perspective, this application may be approved when agreement is reached on product labeling.

Michelle M. Chuen, M.D.
January 25, 2007

cc: NDA #21-977
HFD-130 (Div. File)
HFD-130/MChuen
/TLaughren
/MMathis
/NKhin
/FCurtis

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/s/

Michelle Chuen
1/25/2007 12:11:36 PM
MEDICAL OFFICER

Ni Aye Khin
1/31/2007 06:01:45 PM
MEDICAL OFFICER

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approvable action for lisdexamfetamine (NRP-104) capsules for the treatment of attention deficit hyperactivity disorder (ADHD)

TO: File NDA 21-977
[Note: This overview should be filed with the 12-6-05 original submission of this NDA.]

1.0 BACKGROUND

NRP104 is a prodrug for d-amphetamine. When taken orally, NRP104 is converted to d-amphetamine mostly by first-pass, and to a lesser extent systemically. There would be expected to be very little conversion by the intravenous route. Thus, the sole rationale for this product, relative to other products in the stimulant class, is to decrease the risk of abuse. Conversion by the oral route would presumably limit abuse by this route because of saturation of the enzymes involved in conversion. As noted, conversion by the IV route is even less efficient. [redacted] The recommended dose range for this product is 30 to 70 mg/day; it would be available in strengths of 30, 50, and 70 mg.

This product was developed under IND 67,482, and we held both EOP2 and preNDA meetings with the sponsor.

2.0 CHEMISTRY

I am not aware of any CMC issues that would preclude an approvable action for this NDA. However, there are sufficient CMC deficiencies to preclude a first cycle approval action. The application is missing certain stability data and justification for the proposed retest period. There are some discrepancies that need to be explained, and in general, the impurity specifications need to be tightened. These are all issues that should be resolvable, but will take some time.

3.0 PHARMACOLOGY

I am not aware of any pharm/tox issues that would preclude an approvable action for this NDA. There are [redacted] impurities that the primary pharm/tox reviewer wanted either eliminated or qualified. Dr. Rosloff has argued against requiring qualification, and I agree with his reasoning on this matter. In any case, if the specifications can be tightened as chemistry has requested, this issue may go away.

4.0 BIOPHARMACEUTICS

As noted, following oral administration, NRP104 is converted to d-amphetamine, with a Tmax of approximately 3.5 hours for d-amphetamine. Thus, this need for conversion of NRP104 to the active substance (d-amphetamine) conveys what might be considered a controlled release property. In fact, NRP104 appears to have a time-concentration profile very similar to Adderall XR, and thus, can be given once a day (unlike immediate release amphetamine). Food does not affect overall absorption of d-amphetamine, however, it does delay Tmax by about 1 hour.

It should be noted that the sponsor has proposed [redacted]

I am not aware of any biopharmaceutics issues that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

There were 2 efficacy trials in children with ADHD (aged 6 to 12) that were the focus on the clinical and statistical reviews: (1) 301, a 4-week parallel group study looking at 3 fixed doses on NRP104 (30, 50, and 70 mg/day) vs placebo, and (2) 201, a laboratory classroom study with a crossover design that looked at 3 groups (optimal dosing with NRP104, optimal dosing with Adderall XR, or placebo).

For study 301, the primary endpoint was change from baseline on the ADHD-RS (LOCF) at week 4. The results strongly favored all 3 dose groups vs placebo ($p< 0.001$ in all cases). There was a numerical trend suggesting weak dose response for efficacy (mean change from baseline was 22, 23, and 27 for the 30, 50, and 70 mg/day dose groups, respectively), but these differences were not statistically significant and are modest, at best. Thus, there is no compelling evidence for any advantages to doses higher than 30 mg/day. The sponsor proposes

[redacted]

For study 201, patients were first titrated to their optimal dose on Adderall XR, and then randomized to that dose of Adderall XR, to what was considered a comparable dose of NRP104 (the conversions were 30, 50, and 70 mg/day of NRP104 for 10, 20, and 30 mg/day of Adderall XR), or to placebo. The primary endpoint was the SKAMP Deportment Score averaged across all 8 timepoints for the assessment day. Both active drug treatment groups were strongly superior to placebo on the primary endpoint ($p< 0.001$). The sponsor proposes [redacted]

[redacted]

5.2 Safety Data

The safety review for this product was based on 11 clinical studies: 5 clinical pharmacology studies, 3 phase 3 studies (2 completed and 1 ongoing), and 3 abuse liability studies. The adverse events profile for this drug is the common profile seen with other stimulants, i.e., there were no new serious adverse events detected. This drug, if approved, will get the new warning language for cardiovascular and psychiatric events of possible concern.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling.

[redacted]

[redacted]

6.0 FOREIGN REGULATORY ACTIONS

To my knowledge, NRP-104 is not approved anywhere at this time for the treatment of ADHD.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

8.0 DSI INSPECTIONS

Inspections were conducted at 3 sites, and the data were judged to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

9.1 Labeling

We have included an extensively modified version of labeling with the approvable letter.

9.2 Approvable Letter

The approvable letter includes our proposed labeling and requests for responses to a number of questions that were raised during the course of the review that the sponsor has not addressed as yet, including several CMC questions.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that New River Pharmaceuticals, Inc. has submitted sufficient data to support the conclusion that NRP1-4 is effective and acceptably safe in the treatment of ADHD. However,

before we can take an approval action, the sponsor needs to respond to various requests we have made and we need to reach agreement on labeling. Thus, we recommend issuing the attached approvable letter along with our proposal for labeling, in anticipation of final approval. As noted, DEA will make the ultimate determination about controlled substances classification, and this determination must be made before this product can be marketed.

cc:
Orig NDA 21-977
HFD-130
ODE-I/RTemple
HFD-130/TLaughren/MMathis/NKhin/MChuen/FCurtis

DOC: Lisdexamfetamine_Laughren_AE Memo.doc

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/s/

Thomas Laughren
9/28/2006 01:30:12 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 29, 2006

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21-977 (This overview should be filed with the 12-06-2005 original submission.)

SUBJECT: Recommendation of Approvable Action for Lisdexamfetamine (NRP-104) Capsules for the Treatment of Attention-Deficit Hyperactivity Disorder (ADHD)

1. BACKGROUND

Amphetamine products including dextroamphetamine and mixed salts of a single-entity amphetamine (amphetamine/dextroamphetamine) are available in the U.S. for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). These available stimulant products are known to have a high abuse potential and a possibility of obtaining for non-therapeutic use.

The sponsor's development program of NRP104 is intended for its use in the treatment of ADHD. NRP104 is a pro-drug of d-amphetamine. The active ingredient in NRP104 capsules is lisdexamfetamine dimesylate which lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the GI tract, releasing active d-amphetamine. The proposed commercial formulation of NRP104 is a capsule containing 30 mg, 50 mg or 70 mg of the pro-drug lisdexamfetamine.

IND 67,482 for NRP-104 was originally submitted on 10/16/2003 by New River Pharmaceuticals, Inc. An EOP2 meeting was held on 7/29/2004. The discussion included:

- Agreement with additional pharmacokinetic studies
- Overall design of the two proposed pediatric phase 3 studies
- The statistical approach and definition of the efficacy population

At the pre-NDA meeting with the sponsor on 7/6/2005, the clinical issues addressed included:

- A summary of vital signs
- Inclusion of weight in the vital sign assessments
- Requirements for NDA

The sponsor submitted the above referenced NDA on December 6, 2005. The application included the efficacy results from two clinical studies 201 and 301.

This NDA has been reviewed by Yeh-Fong Chen, Ph.D., from the Office of Biostatistics (review dated 07/27/2006), and Michelle Chuen, M.D., Medical Officer, DPP (review dated 07/28/06). The

Office of Clinical Pharmacology (OCP) review was conducted by Andre Jackson, Ph.D. (review dated 8/4/06). The CMC reviewer is Lyudm Soldatova, Ph.D. The pharmacology/toxicology reviewer is Ikram Elayan, Ph.D. At the time of completion of this memo, the Chemistry and the Pharmacology/Toxicology reviews are not finalized.

2.0 CHEMISTRY

Thomas Oliver, Ph.D., Chemistry Team Leader, has mentioned that there are substantial CMC concerns that need to be addressed prior to taking an approval action. However, I am not aware of any CMC concerns that would preclude an approvable action on this NDA.

3.0 PHARMACOLOGY

I am not aware of any pharmacology/toxicology issues that would preclude an approvable action for this NDA.

4.0 CLINICAL PHARMACOLOGY

The clinical pharmacology review covered the results from 4 clinical pharmacology studies (NRP104.101; NRP104.102, NRP104.103 and NRP104.104). The sponsor has conducted these studies for an assessment of relative bioavailability to the optimally available oral formulation; for the section of dosages for the pediatric pivotal studies; and for an assessment of the effects of food. I refer to the review by Dr. Jackson for detail.

After oral administration, NRP104 (lisdexamfetamine dimesylate) is rapidly absorbed from the GI tract. During the absorption process, active dextroamphetamine is released as the hydrolyzation of the amide linkage and lysine cleavage occurred. The major metabolite of NRP104 in plasma is d-amphetamine. The Tmax of d-amphetamine was approximately 3.5 hr (fasting) whereas the Tmax of lisdexamfetamine dimesylate was approximately 1 hour. The $t_{1/2}$ is approximately 9 hrs for NRP104. The Cmax and AUC values of the parent drug NRP104 were decreased by 45% and 12%, respectively, in the fed state compared with the fasting condition. There is no appreciable effect of food on the d-amphetamine metabolite. Exposure of the metabolite d-amphetamine is 16 fold higher than that of the parent drug NRP104. The PK for the intact NRP104 exhibited nonlinear kinetics over 30-70 mg dose while the d-amphetamine metabolite exhibited dose proportional kinetics. The AUC and Cmax for d-amphetamine from 75 mg NRP104 were comparable to both d-amphetamine and l-amphetamine from 35 mg Adderall XR. The evaluation of the content of NRP104 capsules in the form of d- and l-amphetamine showed that there were apparent differences in the d-amphetamine between Adderall XR 35 mg and NRP104 75 mg, [redacted] mg and [redacted] mg, respectively.

[redacted]

The OCP review provided labeling changes to the labeling proposed by the sponsor. There was no issues identified that would preclude an approvable action for this NDA.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was based on the results of one double-blind, placebo-controlled, fixed dose study (study 301) and one crossover study (study 201) to evaluate the efficacy and safety of NRP104 in treatment of ADHD in pediatric population.

The sponsor indicated that results of these 2 clinical studies demonstrated that all doses of NRP104 tested were superior to placebo on the primary efficacy variable. I would briefly describe the results of each of these studies pertinent to efficacy claim in the following subsection.

5.1.2 Summary of Studies Pertinent to Efficacy Claim

Study 301

This was a multicenter, randomized, double-blind, placebo-controlled study comparing three fixed doses of NRP104 (30mg, 50mg, or 70mg) vs. placebo. This study enrolled patients between 6 to 12 years of age, with a DSM-IV-TR diagnosis of ADHD. After a 1-week washout of previous stimulant treatment, eligible subjects were randomized to receive NRP104 (30, 50 or 70 mg given as oral capsules once daily in the morning) or placebo for 4 weeks of treatment. All subjects in the NRP104 group received 30 mg of NRP104 for study week 1. For those subjects in the 50 mg, the study drug was increased to 50 mg at study week 2 and received the 50 mg dose until end of the study. For those subjects randomized to the 70 mg NRP104 treatment, the dose of NRP 104 was 50 mg at study week 2, and 70 mg at study week 3 and 4.

The study was conducted at 64 centers in the U.S. The total number of subjects enrolled in this study was 297; 290 subjects were randomized to the double-blind treatment in which 218 subjects in the NRP104 treatment group. The ITT samples (total N=285) for NRP104 30 mg, 50 mg, 70 mg, and placebo were 69, 71, 73, and 72, respectively. The subjects enrolled were mostly Caucasian (46-59%), mean age was approximately 9 yrs, had approximately 70% male subjects, and 95% were diagnosed with ADHD-Combined Type. There seemed to be no significant differences in demographic characteristics among the treatment groups. A total of 230 subjects (97%) completed the study; 67 subjects discontinued. The most common reasons for discontinuation from the study were adverse events (a higher percentage in NRP104 treatment groups), lost to follow up (esp. prior to randomization), and lack of efficacy (more dropouts due to this reason in placebo group).

The primary efficacy variable was the ADHD Rating Scale [ADHD-RS (Version IV)] which was assessed at baseline and at each weekly study visit. Secondary variables included Conner's Parent Rating Scale and CGI-I, but there were no key secondary variables identified in the protocol. The primary end point was the change from baseline of the ADHD-RS total score at the last post-randomization treatment week (i.e., week 1 through week 4) for the LOCF dataset. The ANCOVA was the statistical model employed, with terms for treatment, site, and the baseline score as the

covariate. For multiple comparisons for 3 doses of NRP 104 vs. placebo, the statistical testing was carried out using the Dunnett's test with LS mean adjustment. Dr. Chen confirmed the efficacy results. Analyses were also done using the mixed effects model (MMRM).

Efficacy Results on SKAMP-DS Scores in Study 301 (LOCF):

Treatment Group (number of subjects)	Mean Baseline ADHD-RS Total Scores (SD)	Mean Change from Baseline at Endpoint (SD)	Placebo-adjusted LS mean	P-values (vs. placebo)
NRP104 30 mg (N=69)	43.2 (6.68)	-21.8 (1.6)	-15.58	<0.0001
NRP104 50 mg (N=71)	43.3 (6.74)	-23.4 (1.56)	-17.21	<0.0001
NRP104 70 mg (N=73)	45.1 (6.82)	-26.7 (1.54)	-20.49	<0.0001
Placebo (N=72)	42.4 (7.13)	-6.2 (1.56)	0	-

Comment:

Both Drs. Chuen and Chen considered this a positive study for NRP104, and I agree with them.

Study 201

This was a multicenter, randomized, double-blind, three-treatment, three-period, cross-over study. This study was conducted in a laboratory classroom setting to evaluate efficacy and safety of NRP 104 (30 mg, 50 mg or 70 mg) in treatment of ADHD in pediatric population. The study consisted of one week screening period, three weeks of dose titration and three weeks of double-blind cross-over period. During the dose-titration period, all enrolled subjects received 10 mg per day of Adderall XR in the first week. In next two weekly visits, based on the investigator's evaluation, Adderall XR dose would remain the same or would be increased to 20 mg for the second week, to 30 mg for the third week. Adderall XR dose at the end of the third titration week was considered as the optimal daily dose and used in the subsequent double-blind phase. The daily dose of the three treatments each randomized subject received over the course of the 3-week double-blind period was based on the conversion in the following table:

Optimal Adderall XR Dose in the Dose-Titration Period	The Treatment Dose received in the Double-Blind, Cross-Over Periods
Adderall XR 10 mg/day	NRP104 30mg/day, Adderall XR 10 mg/day or Placebo
Adderall XR 20 mg/day	NRP104 50mg/day, Adderall XR 20 mg/day or Placebo
Adderall XR 30 mg/day	NRP104 70mg/day, Adderall XR 30 mg/day or Placebo

During each double-blind week, subjects took the treatment dose every morning at home for the first 6 days, and the day 7 dose was administered at the laboratory school visit on day 7 as they returned on day 7 of each week for a laboratory classroom assessment at time points specified in the protocol (i.e., 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours post-dose).

The study was conducted at 4 centers in the U.S. The total number of subjects enrolled in this study was 52; all 52 subjects were randomized to the double-blind treatment from which 50 subjects completed the study. The ITT samples was N=50. The subjects enrolled were 56% Caucasian, 23% African American; mean age was 9.1 yrs; and had approximately 63% male subjects. The

reason for discontinuation from the study was lost to follow up for 1 subject and adverse event for the other subject.

The primary efficacy variable was the Swanson, Kotkin, Aglar, M.Flynn and Pelham (SKAMP) Deportment Scores rated by the investigator. Secondary variables included SKAMP-Inattention and CGI-I, but there were no key secondary variables identified in the protocol. The primary end point was the average of SKAMP-DS across the treatment assessment day.

The mixed-effects ANOVA was the statistical model employed in performing defined treatments and periods. The treatment levels were NRP104 (30, 50 and 70mg combined), Adderall XR (10, 20 and 30 mg combined), and placebo. Pair-wise comparisons of least square means between the individual treatments were further conducted using a t-test. The non-parametric Wilcoxon Signed Rank test was also to be utilized to perform the pair-wise comparisons if statistical assumptions of the ANOVA were not satisfied. A simple-1 way ANOVA was to be utilized to assess the differences among the three treatments if inconsistency in treatment effect was noted.

A significant difference in patient behavior, based upon the average of investigator ratings on the SKAMP-DS scores across the 8 sessions of a treatment day, was observed between NRP104 and placebo. Dr. Chen confirmed the efficacy results. The primary efficacy results are as follows:

Efficacy Results on SKAMP-DS Average Scores in Study 201:

Treatment Group (N=50)	Mean Change (SD)	LS mean (SD)	Difference in LS Mean (vs. placebo)	P-values (vs. placebo)
NRP104	0.8 (0.7)	0.8 (0.1)	-0.9	<0.0001
Adderall XR	0.8 (0.8)	0.8 (0.1)	-0.9	<0.0001
Placebo	1.7 (1.2)	1.7 (0.1)		

Comment:

Both Drs. Chuen and Chen considered this a positive study for NRP104 and I agree with them.

5.1.3 Comments on Other Important Clinical Issues

Subgroup Analyses

Since the study 201 was a small study (N=50), the sponsor performed exploratory subgroup analyses only for study 301 in order to detect subgroup interactions on the basis of gender (boys vs. girls), age (6- yrs.; 10-12 yrs) and race (Caucasians vs. non-Caucasians). Dr. Chen confirmed the sponsor's analysis.

As can be seen in Dr. Chen's review, there were no differences in the ADHD-RS scores among the treatment groups at baseline for boys but the differences was statistically significant among the treatment groups for the girls. All treatment groups, including placebo, showed improvement from baseline to endpoint for boys and girls. For both genders, the score reduction in the 50, and 70 mg groups was observed to be statistically significantly larger than in the placebo group. There were no differences in the ADHD-RS at baseline among the treatment groups for both age populations. All treatment groups, including placebo, showed improvement from baseline to endpoint in both age populations. For both age populations, the score reduction in the 30-, 50- and 70- groups was statistically significantly larger than in the placebo group. There were no differences in the ADHD-RS at baseline among the treatment groups for both race groups. All treatment groups, including placebo, showed improvement from baseline to endpoint in both ethnicity/race populations. For the group of Caucasian subjects, the score reduction in the 30-, 50- and 70- mg groups were statistically significantly larger than in the placebo group. However, for the group of non-Caucasian subjects, only the score reduction in the 50- and 70-mg groups were statistically significantly larger than in the placebo group.

Secondary Efficacy Variables

As stated above, there were no key secondary variables identified in both studies. I did not see any documentation that the sponsor had a pre-specified analysis plan declaring any of the secondary variables listed as key secondary efficacy variable.

Duration of Treatment

The studies were conducted for short-term use of NRP104 in the treatment of ADHD. There is no data pertinent to the long-term (more than 4 weeks) efficacy of NRP104 in this submission.

5.1.4 Conclusions Regarding Efficacy Data

In summary, the efficacy analyses of both studies supported the efficacy claim of NRP 104 in the treatment of ADHD in all dose groups tested.

5.2 Safety Data

5.2.1 Satety Database

Dr. Chuen's safety review of this NDA was based on an integrated database covering 11 clinical trials in the drug development program for NRP104. This included:

1) 5 phase 1 clinical pharmacology studies
2) 3 phase 2/3 clinical studies

- 2 completed phase 3 double-blind studies in subjects with ADHD (study 201 and 301)
- 1 ongoing phase 2/3 study (study 302)

3) 3 abuse liability studies

Dr. Chuen's safety review included data from the original submission and a 4-month safety update with the data cut-off date of 7/15/2005 and 01/16/2006, respectively.

A total of 272 subjects were treated with NRP104 and 124 subjects received placebo. Out of the 272 subjects treated as of 1/16/06, 62 subjects completed, 118 subjects discontinued at post-baseline, 92 subjects are ongoing in the study 302, an open-label safety study of follow-up up to one year.

There were no deaths reported. Serious adverse events were available from these trials. 4 subjects of the NRP104 treated patients in the clinical studies experienced SAE. Two SAEs (mania and agitation) experienced by a 13 yr old male subject who received 70 mg dose of NRP104. The overall dropout rates were similar across the treatment groups (NRP104 30mg: 21.1%; NRP104 50mg: 18.9%; NRP104 70mg: 17.8%; placebo: 25%. The common reasons for discontinuation from the study included adverse events and lost to follow up in the NRP104 group; and unsatisfactory response in the placebo group. There were no post-marketing data since this drug is not marketed any country in the world.

5.2.2 Safety Findings and Issues of Particular Interest

5.2.2.1 Common and Drug-Related Adverse Events

The approach that we have used to identify the adverse event profile is by identifying the adverse events for the drug as common (used 5% as the cut-off) and considered as drug related (a risk for drug that is twice or more the placebo risk). These AEs included upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight. There were no subjects reported to experience euphoric mood in phase 2/3 studies while 6 subjects (10.7%) of NRP104 subjects reported euphoric mood in the phase 1 studies.

The sponsor evaluated the relationship between dose and the reporting incidence of treatment emergent AE. AEs examined were those reported by at least 5% of NRP104 treated subjects in any dose group or in all subjects treated with NRP 104. Dose groups were: 30 mg (N=71); 50 mg (N=74); and 70 mg (N=73). There is a trend of dose-relatedness for AEs of vomiting, nausea, dry mouth, decreased appetite, decreased weight, headache, and insomnia.

5.2.2.2 Cardiovascular and Psychiatric Adverse Events

There were no deaths reported in the NRP104 studies. As stated by Dr. Chuen in her review, she searched all AEs of study 301 for events possibly related to mania and agitation. There were no cases of mania in any of the treatment groups. The incidence of agitation in the NRP104 50 mg treated group was 2.7% (2/74) while there were no cases of agitation in the placebo-treated group (0/71).

The Agency has recently requested the sponsors of stimulants to provide for revisions to the WARNINGS Section of the Package Insert that serious cardiovascular events including reports of sudden deaths in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In addition, there are also revisions in the labeling regarding the psychiatric adverse events subsection including exacerbation of pre-existing psychosis, possible induction of mixed/manic episodes, emergence of new psychotic or manic symptoms and aggression. We will ask the sponsor of NRP104 to include pertinent information regarding these cardiovascular and psychiatric events to the labeling.

5.2.2.3 Vital Signs and ECG Data

A mean increase from baseline in heart rate was observed between NRP104 and placebo (p=0.0224). It was dose-dependent with greatest effect generally observed in the high dose group (i.e., NRP104 30mg: 0.3 bpm; 50mg: 2.0 bpm; 70 mg: 4.1 bpm compared to -0.7 bpm in placebo). Similarly, mean changes from baseline to final on-therapy assessment were statistically significantly different between NRP104 and placebo for heart rate, RR and QRS interval based on the ECG data obtained in study 301. A modest increase in average heart rate (about 3-6 bpm) and average blood pressure (about 2-4 mmHg) is noted in the Warnings section of standard stimulant labeling. We will modify the NRP104 labeling to include this standard language.

5.2.2.4 Laboratory Tests

There were statistically significant differences in mean changes from baseline to endpoint in laboratory parameters in terms of hematology (eosinophils, hematocrit, hemoglobin, RBC, neutrophils and lymphocyte counts) and chemistry (albumin, BUN, Calcium and ALT) between NRP104 and placebo. These mean changes appear to be small and unlikely to be clinically significant. The differences in changes in alkaline phosphatase seemed large, i.e., NRP104 30mg, 50mg, 70mg vs. placebo: -24.09, -14.57, -26.25, -2.1 IU/L, respectively, although clinical significance of this finding is unclear.

5.2.2.5 Height and Weight Changes

For study 301, the mean changes from baseline to final on-therapy assessment were statistically significant between NRP 104 and placebo for weight; -0.9 (30mg), -1.9 (50mg), -2.5 lb (70mg) vs. 1.0 lb (placebo). The sponsor did not make adjustment for age and gender on this data. Weight loss is not an unexpected finding with stimulant treatment (i.e., -1.1 to -2.8 lb within the initial 4 weeks of therapy with amphetamine products). We will ask the sponsor to include the standard language on long-term suppression of growth subsection in the labeling.

5.2.2.6 Abuse Liability and Controlled Substance Schedule

The Controlled Substance Staff (CSS) conducted their 8 factor analysis on abuse liability. In their preliminary draft review dated 8/21/06, it is recommended that lisdexamfetamine be controlled in Schedule II of the Controlled Substance Act. Final Schedule of this drug is yet to be determined by the DEA.

5.2.3 Conclusion Regarding Safety of NRP104

Overall, this submission revealed safety findings of NRP104 consistent with the previously observed safety profile of amphetamines. No specific safety concerns raised by the clinical reviewer. There are no recommendations for further study. There were a number of items as outlined in Dr. Chuen's review as well as in previous clinical information request letter to which the sponsor has not responded yet. We may reiterate these items in the action letter.

6.0 WORLD LITERATURE

The sponsor did not perform literature search. Although the Division has requested in the information request email dated 3/1/06, the sponsor has not submitted any data from literature search pertaining to the safety and efficacy of NRP104.

7.0 FOREIGN REGULATORY ACTION

To my knowledge, this drug is not approved for any indication in any country at this time. We will ask for an update on the regulatory status.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this NDA to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 3 study sites. DSI recommended that data from these inspected sites appear acceptable in support of this NDA. Inspectional findings did not seem to raise any major concern on integrity of study data.

10.0 LABELING AND ACTION LETTER

10.1 Final Draft of Labeling Attached to the Action Package

The sponsor's proposed language has been modified. Our proposed labeling should be included in the action letter.

10.2 Foreign Labeling

At this time, I am not aware that NRP104 is approved for the treatment of ADHD anywhere else.

11.0 CONCLUSION AND RECOMMENDATION

The sponsor has submitted sufficient data to support that NRP104 is effective and reasonably safe in the treatment of ADHD in pediatric population (6-12 yrs of age). I recommend that we issue an approvable action letter. We may consider approval of this NDA provided that the sponsor responds adequately to the CMC concerns, and upon receipt of an agreement between the sponsor and the Agency regarding the language in the labeling.

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/s/

Ni Aye Khin

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-977
Submission Code	N
Letter Date	December 6, 2005
Stamp Date	December 6, 2005
PDUFA Goal Date	October 6, 2006
Reviewer Name	Michelle M. Chuen, M.D.
Review Completion Date	July 28, 2006
Established Name	Lisdexamfetamine Dimesylate Capsules
Trade Name	None
Therapeutic Class	Amphetamine
Applicant	New River Pharmaceuticals, Inc.
Priority Designation	S
Formulation	30, 50, and 70mg Capsules
Dosing Regimen	30-70 mg/day
Indication	Attention Deficit Hyperactivity Disorder
Intended Population	Children with Attention Deficit Hyperactivity Disorder

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement be granted approvable status. There are a number of requests[1] to which the sponsor has not yet responded. These responses will be reviewed in an addendum. In addition, it is recommended that further information be requested (see section 9.2). Final approval is contingent on satisfactory responses to the concerns conveyed in previous requests for information and in the approvable letter, satisfactory Final Clinical Study Report for Study 302, satisfactory DSI, CSS, Statistical, CMC, Pharm/Tox, and Biopharm reviews, and mutual agreement on labeling (see section 9.4).

1.1.1 Risk Management Activity

There are no additional recommendations.

1.1.2 Required Phase 4 Commitments

There are no additional recommendations.

1.1.3 Other Phase 4 Requests

There are no additional recommendations.

1.2 Summary of Clinical Findings

1.2.1 Brief Overview of Clinical Program

The efficacy of oral lisdexamfetamine dimesylate (also referred to as NRP104) in the treatment of patients with attention deficit hyperactivity disorder (ADHD) is based on Studies 201 and 301.

[1] These requests are summarized as follows: 1) literature search, 2) enumeration of pre-marketing adverse events not reported in the >2% Table for the Safety Populations of Studies 201 and 301, 3) enumeration of ITT population patients using concomitant medications during the double-blind period of Study 201 and during Study 301, 4) enumeration of patients that were identified as protocol violators because of prohibited medication use for Studies 201 and 301, 5) serious adverse event definition, 6) mean change from baseline analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, 7) outlier analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, and 8) description of height and weight measurement methodology

Study 201 consisted of a 3-week Adderall XR open-label titration period followed by a randomized, double-blind 3-treatment, 3-period (one week each) double-blind fixed dose crossover period utilizing NRP104 doses of 30, 50, and 70 mg/day, Adderall XR doses of 10, 20, and 30 mg/day, and placebo. Study 301 was a randomized, double-blind, placebo-controlled, fixed dose trial of about 4 weeks' duration utilizing doses of 30, 50, and 70 mg/day.

The safety of NRP104 is based on Study 301, in which safety was evaluated in 218 NRP104 patients and 72 placebo patients. Deaths, serious adverse events and dropouts due to adverse events were examined for an additional 186 patients in the remaining ten studies (studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03).

1.2.2 Efficacy

The sponsor has provided evidence from one crossover study (Study 201) and one parallel-group study (Study 301) with three doses of (30, 50, and 70 mg/day) that supports the claim of short-term efficacy for the use of NRP104 in attention deficit hyperactivity disorder. The primary efficacy variables in Studies 201 and 301 were the SKAMP-DS and the ADHD-RS, respectively.

1.2.3 Safety

A total of 404 patients received NRP104 and had safety data in eleven trials. Since Study 302 is still ongoing, complete safety data for this study is pending at this time. This submission revealed safety findings consistent with the previously observed safety profile of amphetamines.

1.2.4 Dosing Regimen and Administration

Study 301 was a fixed dose study of NRP104 that examined doses of 30, 50, and 70 mg/day versus placebo in the treatment of attention deficit hyperactivity disorder. All three dose groups produced a significant difference over placebo.

Patients were randomized to 30, 50, and 70 mg treatment groups. For all dose groups, dosing for NRP104 began at 30 mg/day for the first week of treatment. For the 50 and 70 mg treatment groups, dosage was increased to 50 mg/day at week 2. For the 70 mg treatment group, dosage was increased to 70 mg/day at week 3.

Based on drug/placebo comparisons, there was evidence of a significant treatment effect for the low dose ($p<0.0001$), and results at the two higher doses were similar in both robustness ($p<0.0001$) and magnitude of effect size (placebo-adjusted difference of -15.58, -17.21, and -20.49 for 30 mg, 50 mg, and 70 mg, respectively). The mean change from baseline at endpoint was -21.8 (SE=1.60), -23.4 (SE=1.56), and -26.7 (SE=1.54) for the 30 mg, 50 mg, and 70 mg groups, respectively. The difference between the 30 mg and 70 dose groups could be as small as 0.2 on a 54-point scale, which is unlikely to be clinically significant. Therefore, there appears to be no substantial advantage of the higher doses (50 and 70 mg) over the lower dose (30 mg).

In Study 201, since patients were not randomized to fixed doses in this trial, no assessment of dose-response was possible.

1.2.5 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

1.2.6 Special Populations

Age did not appear to significantly affect treatment response as measured by SKAMP-DS average and ADHD-RS change from baseline for Studies 201 and 301, respectively. Ethnicity appeared to affect treatment response for Study 301, but not for Study 201. There was insufficient information to determine the effect of gender or baseline severity of illness on outcome. Please see Section 6.1.4 for further details.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

NRP104 is a novel product being developed as a once-a-day treatment for attention deficit disorder (ADHD) in pediatric populations (ages 6-12). The active ingredient in NRP104 capsules is lisdexamfetamine as the dimesylate salt, a new chemical entity. In its intact form lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. Lisdexamfetamine is an amide conjugate comprised of L-lysine covalently bound to the amino group of d-amphetamine.

The sponsor is seeking approval for treatment of children (ages 6-12) with attention deficit hyperactivity disorder (ADHD) with a dosing regimen of 30 to 70 mg/day based on the results of 2 completed clinical studies (1 Phase 2, 3-period crossover and 1 short-term fixed-dose).

2.2 Currently Available Treatment for Indications

The five moieties approved in the U.S. for the treatment of attention deficit hyperactivity disorder are: dextroamphetamine, mixed salts of a single entity amphetamine product (amphetamine/dextroamphetamine), methylphenidate, dexmethylphenidate, and atomoxetine.

2.3 Availability of Proposed Active Ingredient in the United States

Lisdexamfetamine has not been approved for use in the United States.

2.4 Important Issues with Pharmacologically Related Products

NRP104 is most closely related pharmacologically to dextroamphetamine and mixed salts of a single entity amphetamine product (amphetamine/dextroamphetamine). These products have been associated with several safety issues. Among the major safety issues are sudden death with structural cardiac abnormalities or other serious heart problems, hypertension, tachycardia, psychotic symptoms, manic symptoms, aggressive behavior or hostility, long-term suppression of growth, seizures, and visual disturbance.

2.5 Presubmission Regulatory Activity

An end-of-Phase 2 meeting request to discuss the development of NRP104 in the treatment of ADHD was submitted May 6, 2004, and the meeting was held on July 29, 2004. At the meeting, clinical issues addressed included: 1) agreement with additional pharmacokinetic studies, 2) concurrence with the overall design of the two proposed pediatric pivotal Phase 3 studies[2], 3) concurrence with the statistical approach and definition of the efficacy population, and 4) agreement that the overall clinical development plan was adequate and supported registration of the product for the treatment of ADHD in 6-12 year olds.

At the pre-NDA meeting on July 6, 2005, among the clinical issues addressed were the Agency's requests for 1) a summary of vital signs, 2) inclusion of weight in the vital signs assessments, 3) further breakdown of ethnicity, and 4) calculated z-scores for all longer term studies.

This NDA was submitted to the Agency on December 6, 2005. The Filing Meeting was held on January 24, 2006 and it was concluded that this supplement was fileable. The User Fee due date is October 6, 2006.

A 4-Month Safety Update to the NDA was submitted on April 11, 2006.

2.6 Other Relevant Background Information

The undersigned reviewer was unable to locate any information on withdrawal of the product in other countries, or on submission of marketing authorization applications to foreign regulatory agencies.

[2] Note that, although in the meeting, the sponsor referred to two Phase 3 studies as proposed pivotal studies, the briefing package contained protocols for two short-term efficacy studies [one Phase 2 (Study 201) and one Phase 3 (Study 301)] and one long-term safety study (Study 302).

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

According to a 7/20/06 email from Lyudmila Soldatova, Ph.D., Chemistry reviewer, the sponsor claimed categorical exclusion from Environmental Assessment for this NDA. At the time of completion of this review, neither her CMC review nor a draft of her review was available.

3.2 Animal Pharmacology/Toxicology

At the time of completion of this review, neither a Pharmacology/Toxicology review nor a draft of the review was available. According to a 7/25/06 email from Barry Rosloff, Ph.D., Pharmacology/Toxicology Team Leader, there were no significant pharmacology/toxicology concerns.

3.3 Statistical Review and Evaluation

Yeh-Fong Chen, Ph.D., is the statistical reviewer for this NDA. Her written review is pending completion at this time. Based on a draft of her review, she has indicated that both efficacy studies (201 and 301) demonstrated efficacy of all three doses of NRP104. Nevertheless, she indicated that [redacted] cannot be granted [redacted]

3.4 DSI Clinical Site Inspections

The Division of Scientific Investigations (DSI) selected 3 sites for inspection. Two of the sites were from studies 201 and 301 [site 04 (Dr. Frank Lopez), and site 03 (Dr. Ann Childress)], and one of the sites was from Study 301 [site 37 (Dr. [redacted]]. Inspections for all sites have been completed. However, at the time of completion of this review, a Clinical Inspection Summary has not yet been completed by Jose Tavarezpagan, DSI Consumer Safety Officer.

According to the VAI (Voluntary Action Indicated-no response requested) letter sent to Dr. Childress, records for 11 subjects enrolled in Study 201 and 4 subjects enrolled in Study 301 from site 03 were reviewed by DSI. It was determined that the site did not conduct the investigation in accordance with the investigational plan. Deviations from the protocol included lack of a 30-day follow-up phone call for 2 patients in Study 201, and lack of hematology test at screening for one patient in Study 301. Overall, data generated from protocols NRP104.201 and NRP104.301 at this site appeared acceptable for use in support of this NDA.

Data from the remaining 2 sites for use in support of this NDA supplement is still pending.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The safety of NRP104 in the treatment of pediatric patients with attention deficit hyperactivity disorder is based on Study 301. Deaths, serious adverse events and dropouts due to adverse events were examined for the remaining ten studies (studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03).

The efficacy of NRP104 in the treatment of pediatric patients with attention deficit hyperactivity disorder is based on studies 201 and 301. Study 201 consisted of a 3-week Adderall XR open-label titration period followed by a 3-week, 3-period double-blind fixed dose crossover period. Study 301 was a 4-week fixed dose study.

4.2 Tables of Clinical Studies

A total of eleven clinical trials comprise this application. These trials are summarized in the table below.

TABLE 4.2.1: NRP104 STUDIES

Phase I Studies	
Single-Dose	
102	Open-label, 3-treatment, 3-period, 6-sequence, randomized, crossover study to assess the relative bioavailability of d-amphetamine of NRP104 70 mg in 18 healthy subjects aged 18 to 55 when administered orally under 3 dosing conditions: an intact capsule only, a solution containing the capsule contents, and an intact capsule with high fat meal
101	Open-label, randomized, two-period crossover study to compare the rate of absorption and oral bioavailability of two dose levels (25 and 75 mg) of NRP 104 test formulation to oral doses of Dexedrine 30 mg and Adderall XR 35 mg in 20 healthy subjects aged 18 to 55
106	Open-label study to assess the distribution, metabolism, and elimination of NRP-104 radiolabel with ^{14}C in 6 healthy subjects aged 18 to 55
103	Open-label, 3-treatment, 3-period, 6 sequence, randomized, crossover study to asses dose proportionality of d-amphetamine after oral administration of 30, 50, and 70 mg of NRP104 after an overnight fast in 18 children with ADHD aged 6 to 12
Multiple-Dose	
104	Open-label study to assess steady state pharmacokinetics of NRP104 70 mg following 7-day once-daily administration in fasting 12 healthy subjects aged 18 to 55

Completed Phase 2/3 Studies	
201	Multi-center, randomized, double-blind, 3-treatment, 3-period (one week each) crossover study following an 3-week, open-label Adderall XR titration period to assess, in a controlled environment, the efficacy and safety of NRP104 (30, 50, or 70 mg) and Adderall XR (10, 20, or 30 mg) compared to placebo in 52 children with ADHD aged 6 to 12
301	Multi-center, randomized, double-blind, placebo-controlled, parallel-group fixed-dose, 4 week study to assess the efficacy and safety of NRP104 (30, 50, or 70 mg) compared to placebo in 297 children with ADHD aged 6 to 12
Ongoing Phase 2/3 Study	
302	Multi-center, open-label, and single-arm study to assess the safety of NRP104 (30, 50, or 70 mg) for up to one year in children with ADHD aged 6 to 12. As of the NDA submission, 273 patients have been enrolled.
Abuse Studies	
A01	Single-center, single-blind, 2 month study to determine the safety and tolerability of increasing single oral doses of NRP104 (up to 150 mg) compared to placebo and d-amphetamine sulfate 40 mg and to gather preliminary estimates of abuse liability in 12 subjects with a history of stimulant abuse aged 18 to 55
A02	Single-center, double-blind, randomized study to determine the safety, tolerability, and abuse liability of single intravenous doses of NRP104 25 and 50 mg compared to placebo and d-amphetamine sulfate in 12 subjects with a history of stimulant abuse aged 18 to 55
A03	Single-center, double-blind, randomized, placebo-controlled, six-period crossover study to determine whether the abuse potential of NRP104 (50, 100, and 150 mg) is less than that of immediate release d-amphetamine sulfate 40 mg and diethylpropion hydrochloride 200 mg in 36 patients with a diagnosis of stimulant abuse aged 18 to 55

4.3 Review Strategy

A listing of the items examined during the course of this review is provided in Table 4.3.1. The study reports for the Phase 1 studies (102, 101, 104, 106, 103, and 302), the ongoing study (302), and the abuse studies (A01, A02, and A03) were examined for major safety findings only.

TABLE 4.3.1: ITEMS UTILIZED IN THE REVIEW

Submission Date	Items Reviewed
December 6, 2005	Clinical Study Reports: Studies 201 and 301 Proposed Labeling Financial Disclosure Certification Application Summary Case Report Tabulations (.xpt files) Case Report Forms
March 16, 2006	General Correspondence

April 11, 2006	4-Month Safety Update Integrated Summary Case Report Tabulations Case Report Forms Interim Clinical Study Report: 302
June 9, 2006	Clinical Study Report: A03
June 16, 2006	Amendment to a Pending Application: Updated Draft and Annotated Labeling Text
June 29, 2006	Response to FDA Request

4.4 Data Quality and Integrity

The efficacy data from the two positive trials were examined by the statistical reviewer, Yeh-Fong Chen, Ph.D., and there were no outliers or sites identified that were felt to be driving the efficacy results. The Division of Scientific Investigations (DSI) chose 3 U.S. sites from the studies 201 and 301 for inspection: Dr. Frank Lopez, Dr. Ann Childress, and Dr. [redacted] This was based on the number of enrollments and the last date of inspection. Results of the DSI inspections are described in section 3.4.

I conducted an audit of adverse event safety data by comparing Case Report Forms (CRF's) and adverse event line listings for consistency of adverse event information across these two documents in a random sample of 2 patients. No Narrative Summaries were provided. Results are described in section 7.2.7 of this review.

4.5 Compliance with Good Clinical Practices

Studies 201 and 301 were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) according to the International Conference on Harmonization (ICH) guidelines.

4.6 Financial Disclosures

For purposes of this NDA supplement, both studies (201 and 301) are considered "covered clinical stud[ies]" in accordance with 21 CFR 54.2 (e).

Among the clinical investigators in this study, one was identified by New River as having financial arrangements that require disclosure:

[redacted] investigator at study site [redacted], held significant equity interest (in excess of $50,000) with New River Pharmaceuticals, Inc. It is unlikely that

these arrangements biased the study results since this was a double-blind trial and her site contributed only [redacted] patients (about 5%) of the [redacted] patients in the study.

5 CLINICAL PHARMACOLOGY

Please note that a Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review, and the information below was obtained from the sponsor's Summary of Clinical Pharmacology Studies.

5.1 Pharmacokinetics

NRP104 is not metabolized by the liver to form either amphetamine or amphetamine-derived metabolites and there was no significant inhibition by NRP104 of any of the cytochrome P450 isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. There was essentially no hydrolysis of NRP104 by any of the enzymes tested. Although there were trace amounts of d-amphetamine after hydrolysis by Pancreatin and Endopeptidase Lys-C, these were <1% after 4 hours.

After oral administration of ^{14}C NRP104, there was a minimal amount of NRP104 that was essentially cleared by 8 hours after dosing. The majority of radioactivity in the plasma was associated with d-amphetamine and some radioactivity was associated with other moieties, most likely amphetamine metabolites. Essentially all of the ^{14}C was excreted in the urine with trace amount in the feces and excretion was complete within 72 to 96 hours, consistent with the $t_{1/2}$ of d-amphetamine. Approximately 2% of the administered dose of ^{14}C was recovered in the urine as NRP104 and 40% was recovered as amphetamine.

The pharmacokinetics of d-amphetamine was linear over doses of NRP104 ranging from 30 mg to 70 mg in children with ADHD. In healthy adults with histories of stimulant abuse, the pharmacokinetics of d-amphetamine were linear over doses ranging from 30 mg to 130 mg but substantially attenuated between doses of 130 to 150 mg, which the sponsor asserts is consistent with the hydrolysis of NRP104 to d-amphetamine.

Plasma d-amphetamine concentrations reached a three to four fold lower C_{max} at a later T_{max} after intravenous administration of NRP104 than compared to the equivalent dose of d-amphetamine sulfate.

Overall exposure, based on AUC_{∞}, was comparable between 25 mg of NRP104 and 10 mg of d-amphetamine sulfate and 50 mg of NRP104 and 20 mg of d-amphetamine sulfate. The steady-state pharmacokinetics of d-amphetamine after administration of 70 mg NRP104 once daily for 7 days were consistent with those from a single dose.

[3] Number of patients based on Efficacy ITT

Special populations
Within each age group (children and adults), there were no apparent differences between males and females in the dose-normalized C_{max} or AUC for d-amphetamine. There were significant correlations between dose-normalized C_{max} and AUC and body weight. There were no apparent differences in $t_{1/2}$ between male and female subjects, between children with ADHD and healthy adult volunteers, and no apparent relationships between $t_{1/2}$ and either age or body weight.

5.2 Pharmacodynamics

NRP104 is a prodrug of d-amphetamine.

5.3 Exposure-Response Relationships

See Section 8.1 for a discussion of efficacy dose response and Section 7.1.5.6 for a discussion of safety dose response.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This supplemental application seeks to establish the safety and efficacy of NRP104 in pediatric patients with attention deficit hyperactivity disorder.

6.1.1 Methods

The sponsor has conducted two multicenter studies to evaluate the short term efficacy of NRP104 in the treatment of pediatric outpatients with attention deficit hyperactivity disorder (ADHD).

6.1.2 General Discussion of Endpoints

Studies 201 and 301
At the End of Phase 2 meeting on 7/29/04, the sponsor stated that a more detailed statistical analysis plan would be provided to the Agency for comment and input before the database was locked. The Agency stated that the statistical analysis plan should address how they planned to handle drop-outs and dose response. Also, the Agency recommended dosing by mg/kg[4] and the sponsor was told to provide a strategy to determine which dose group was most significant.

At the Pre-NDA meeting on 7/6/05, endpoints were not specifically discussed.

[4] Of note, the sponsor did not follow this recommendation. However, it is difficult to determine how this would have impacted the studies' results.

Study 201
In a 1/18/05 email, the Agency provided statistical comments on the sponsor's statistical analysis plan for Study 201, in which the Agency stated that the trial did not appear to be a pivotal trial. Given the study's crossover design, the Agency advised the sponsor to include suitable washout periods and to test for carryover effect at a prespecified significance level and to prospectively specify an alternative method in the event that the carryover effect was significant. Other concerns regarded the overly strict ITT population definition (requiring patients to have at least 6 sessions' data on Day 7), the suitability of the defined primary endpoint, the lack of consideration of change from baseline as an endpoint, and the lack of incorporation of baseline measurement into the statistical analysis.

In the sponsor's 1/24/05 and 2/3/05 submissions, the sponsor contended that, due to the short (9 hours) half-lives of NRP104 and Adderall XR, there would be no carryover effect. However, the sponsor stated that they would test the 1st order carryover effect in the ANOVA model at a significance level of 0.05 and provide an alternative method if the 1st order carryover effect was found to be statistically significant. The sponsor agreed to modify the definition for the ITT population to include all randomized subjects with at least one SKAMP-DS score post randomization.[5] The sponsor contended that, due to the crossover design of the study (with only one baseline measurement for a given subject receiving all 3 treatments), incorporation of the baseline measurement into the statistical analysis would be considered a violation of the statistical assumption of data independence.

In a 3/30/05 email responding to the sponsor's submissions, the Agency provided statistical comments regarding dealing with missing data in Study 201. The Agency advised that, in addition to calculating the average of 8 sessions of data without considering any missing, they also propose other imputing methods or sensitivity analyses to evaluate the robustness of the analysis results.

The above issues were reviewed by statistical reviewer, Yeh-Fong Chen, Ph.D., and, according to a 7/21/06 email, she stated the sponsor responded satisfactorily to most of our comments regarding Study 201.

Study 301
In a 3/15/05 email, the Agency provided statistical comments on the sponsor's statistical analysis plan for Study 301, in which the Agency asked that the sponsor provide a theoretical justification for the supportive nonparametric ANCOVA approach, propose a plan that controlled the experiment wise type I error rate for all claims sought, propose sensitivity analyses to assess the impact of missing data, ensure that all baseline assessments are complete before randomization (the sponsor's plan to impute a missing baseline score was not considered appropriate), and consider carrying forward the last available value when a particular item was missing (instead of imputing the mean of nonmissing items).

[5] This modification was not noted by the undersigned reviewer in the sponsor's NDA submission.

In a 3/21/05 sponsor submission, the sponsor responded to the Agency's comments.

In a 5/2/05 email, the Agency provided additional statistical comments for Study 301. The Agency stated that it would be a matter of review whether the sponsor's sampling plan was adequate. In addition, the Agency stated that the sponsor's sensitivity analysis approach was unacceptable and the Agency suggested the sponsor use a mixed model analysis for their sensitivity analyses instead.

In the 5/3/05 sponsor submission, the sponsor proposed a mixed effect model with repeated measures for sensitivity analysis.

In a 5/3/05 email, the Agency restated that it would be a matter of review whether the sponsor's [redacted]. The Agency also stated that the proposed mixed effect model was not acceptable for a primary analysis.

The above issues were reviewed by statistical reviewer, Yeh-Fong Chen, Ph.D., and, according to a 7/21/06 email, since the p-values for this study are extremely small, most of the earlier statistical issues are no longer relevant. Regarding the mixed effect model analysis, according to a 7/21/06 email from Dr. Chen, the Agency currently allows sponsors to use it for a primary analysis.

6.1.3 Study Design

Study 201 consisted of a 3-week Adderall XR open-label titration period followed by a randomized, double-blind 3-treatment, 3-period (one week each) double-blind fixed dose crossover period utilizing NRP104 doses of 30, 50, and 70 mg/day, Adderall XR doses of 10, 20, and 30 mg/day, and placebo.

Study 301 was a randomized, double-blind, placebo-controlled, fixed dose trial of about 4 weeks' duration utilizing doses of 30, 50, and 70 mg/day.

These 2 studies will be reviewed separately in Section 10.1.

6.1.4 Efficacy Findings

Predictors of Response
The sponsor performed subset analyses to evaluate the effect of the following variables on treatment response for studies 201 and 301.

- Age (6-9 vs. 10-12 years old)
- Gender
- Ethnicity
- Baseline severity of illness (CGI-S rating of mildly/moderately ill vs. markedly/severely/extremely ill)

Age did not appear to significantly affect treatment response as measured by SKAMP-DS average and ADHD-RS change from baseline for Studies 201 and 301, respectively. Ethnicity did not appear to significantly affect treatment response as measured by SKAMP-DS average for Study 201. In Study 301, the treatment response in non-Caucasians was not significant for 30 mg dose group, and, for the 50 mg dose group, treatment response was significantly less in non-Caucasians than in Caucasians. The Appendices in Section 10.4 present data based on these subgroups.[6]

Of note, in Studies 201 and 301, due to relatively small numbers of female patients, there is insufficient information to determine the effect of gender on outcome. Due to relatively small numbers of markedly/severely/extremely ill patients in Study 201 and relatively small numbers of mildly/moderately ill patients in Study 301, there is insufficient information to determine the effect of baseline severity of illness on outcome.

Size of Treatment Effect
Treatment effect size was examined in terms of SKAMP deportment score average across 8 class sessions on treatment assessment day for Study 201 and in terms of ADHD-RS change from baseline at endpoint for Study 301. The SKAMP-DS average was 0.8 while patients were being treated with NRP104 and 1.7 while patients were being treated with placebo. Although the differences in SKAMP-DS averages were statistically significantly different, the clinical significance of a difference of 0.9 points on a 24-point scale (The SKAMP-DS consists of 4 items with ratings of 0 to 6) is questionable. The ADHD-RS change from baseline at endpoint was -21.8, -23.4, and -26.7 for NRP 30 mg, 50 mg and 70 mg/day patients and -6.2 for placebo patients.

The sponsor has provided evidence from two adequate, well-controlled studies that supports the claim of short-term efficacy for the use of NRP104 in attention deficit hyperactivity disorder (studies 201 and 301).

The results of the two studies are summarized in Table 6.1.4.2 below.

[6] Of note, the sponsor did not perform interaction analyses.

TABLE 6.1.4.2: SUMMARY OF EFFICACY RESULTS (STATISTICAL SIGNIFICANCE OF DRUG/PLACEBO DIFFERENCES AT FINAL ON-THERAPY ASSESSMENT), ITT POPULATION				
Variable	**Study**			
	201 30 mg, 50 mg, and 70 mg doses combined	301 30 mg dose	301 50 mg dose	301 70 mg dose
SKAMP-DS average across 8 sessions	**	NA	NA	NA
ADHD-RS change from baseline at endpoint	NA	**	**	**

Codes: * = significant ($0.01<p\leq0.05$)
**= highly significant ($p\leq0.01$)
NA= not applicable

Duration of Treatment
No study addressing the long-term efficacy of NRP104 in attention deficit hyperactivity disorder has been completed.

6.1.5 Clinical Microbiology

Since NRP104 is a solid oral formulation, this section is not applicable.

6.1.6 Efficacy Conclusions

In summary, the sponsor has provided evidence from one crossover study (Study 201) and one parallel-group study (Study 301) with three doses of (30, 50, and 70 mg/day) that supports the claim of short-term efficacy for the use of NRP104 in attention deficit hyperactivity disorder.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This evaluation of the safety of NRP104 in attention deficit disorder (ADHD) is based on one short-term fixed dose trial (301). Deaths, serious adverse events and dropouts due to adverse events were examined for the remaining ten studies (studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03).

Please see Table 4.2 for a summary of these investigations.

7.1.1 Deaths

There were no deaths.

7.1.2 Other Serious Adverse Events

The undersigned reviewer was unable to locate a serious adverse event definition in the sponsor's Summary of Clinical Safety.[7]

A total of 4 NRP104-treated patients and 0 placebo patients experienced 5 non-fatal adverse events classified as serious. All of these events occurred in patients in study 302. These patients are listed in Table 7.1.2.1 below.

The Narrative Summaries for these patients were reviewed. Two serious adverse events were considered possibly related to NRP treatment: mania and agitation.

I searched the verbatim terms of all adverse events of Study 301 for events possibly related to mania and agitation. There were no cases of mania any of the treatment groups (placebo, NRP104 30 mg, NRP104 50 mg, or NRP104 70 mg). There were no cases of agitation in the placebo-treated group (0/72) or in the NRP104 30 mg-treated group (0/71). The incidence of agitation in the NRP104 50 mg-treated group was 2.7% (2/74). The incidence of agitation in the NRP104 70 mg-treated group was 1% (1/73). The differences between placebo and NRP104 50 mg incidences and between placebo and NRP104 70 mg incidences were not statistically significant (2-tailed Fisher's exact p-value= 0.497 and 1.000, respectively).

[7] This information was requested in a 7/17/06 email.

TABLE 7.1.2.1: NRP104-TREATED PATIENTS WITH SERIOUS ADVERSE EVENTS					
Patient	**Age**	**Sex**	**Days to Onset**	**Dose at time of SAE[8] (mg/day)**	**Serious Adverse Event**
26-2301	12	M	134	70	Splenic injury
27-2314	8	F	138[9]	50	Dehydration
37-2305[10]	13	M	180[11] 205[12]	70	Mania Agitation
41-2304	10	F	Not Provided	70	Gastroenteritis

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Study 301, overall dropout rates were roughly comparable between treatment groups [25% (18/72) of placebo patients, 21.1% (15/71) of NRP104 30 mg patients, 18.9% (14/74) of NRP104 50 mg patients, and 17.8% (13/73) of NRP104 70 mg patients]. Dropout rates primarily due to failure to return [1.4% (1/72) of placebo patients, 5.6% (4/71) of NRP104 30 mg patients, 5.4% (4/74) of NRP104 50 mg patients, and 2.7% (2/73) of NRP104 70 mg patients] were also roughly comparable. Dropout rates primarily due to adverse events were higher in NRP104 patients than in placebo patients [1.4% (1/72) of placebo patients, 8.5% (6/71) of NRP104 30 mg patients, 5.4% (4/74) of NRP104 50 mg patients, and 13.7% (10/73) of NRP104 70 mg patients]. Dropout rates primarily due to unsatisfactory response was highest in placebo patients [16.7% (12/72) of placebo patients, 1.4% (1/71) of NRP104 30 mg patients, 0% (0/74) of NRP104 50 mg patients, and 1.4% (1/73) of NRP104 70 mg patients].

[8] Study 302 was a flexible dose study, and the sponsor did not provide an average daily dose.
[9] Not provided by the sponsor. This number was calculated by the undersigned reviewer given available information.
[10] Of note, the two SAE's for this subject were coded as two episodes of mania in the original (12/6/05) NDA submission and changed to mania and agitation in the 4-Month Safety Update. It was also noted in the narrative that the first SAE of mania was originally reported as suicidal ideation, though there was no other information in the narrative that was consistent with suicidal ideation. In addition, note that the second SAE for this subject occurred after study medication was discontinued on Day 181.
[11] Not provided by the sponsor. This number was calculated by the undersigned reviewer given available information.
[12] Not provided by the sponsor. This number was calculated by the undersigned reviewer given available information.

7.1.3.2 Adverse events associated with dropouts

Appendix 10.5.1 in Section 10.5 presents the incidence of dropouts due to adverse experiences in the Study 301. All twenty-two adverse experiences that led to dropout from NRP104 treatment groups occurred in at least 1% of NRP104 patients at a rate higher than that for placebo patients: ventricular hypertrophy (50 mg and 70 mg groups), upper abdominal pain (30 mg group), dry mouth (70 mg group), vomiting (70 mg group), chest pain (30 mg group), viral upper respiratory tract infection (50 mg group), decreased weight (70 mg group), decreased appetite (30 and 70 mg groups), neck pain (70 mg group), dizziness (30 mg group), lethargy (70 mg group), psychomotor hyperactivity (50 and 70 mg groups), somnolence (70 mg group), abnormal behavior (50 mg group), anger (30 mg group), flat affect (30 mg group), insomnia (30 and 70 mg groups), logorrhea (50 mg group), tic (50 and 70 mg group), pruritis (50 mg group), rash (70 mg group), and hypertension (70 mg group). No single adverse event led to dropout in greater than 2% of the NRP104 30 mg and NRP104 50 mg groups. Two adverse events led to dropout in greater than 2% of the NRP104 70 mg group: vomiting and rash. No adverse events leading to dropout were serious adverse events.

In Phase I studies, there were 2 out of 74 (2.7%) subjects who were terminated due to adverse events (pharyngitis after a single dose of 30 mg and tachycardia after receiving the first dose of 70 mg). In the three abuse studies, no subjects were terminated due to an adverse event.
A tabulation of treatment-emergent adverse events that led to dropout in the pool of Phase II and III studies was examined.[13] There were two adverse events (chest pain and neutropenia) leading to dropout that were concerning. Since the sponsor did not provide patient numbers or narratives for these adverse events, the undersigned reviewer was unable to examine further details regarding these adverse events to see if they were serious adverse events.

7.1.3.3 Other significant adverse events

To assess TEAEs associated with drug abuse potential, the sponsor presented the incidence of euphoric mood as a TEAE of special interest. In Phase I studies, there was a total of 6 (10.7%) NRP104 subjects who reported euphoric mood, and in Phase II/III studies, no subjects reported euphoric mood.

No other clinically significant adverse events were reported.

7.1.4 Other Search Strategies

No other search strategies were reported.

[13] Appendix Table 6.12 of the Summary of Clinical Safety and Table 14 of the Interim Clinical Study Report for Study 302 included in the 4-Month Safety Update

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event data were obtained by observation and close monitoring of all subjects throughout the study. All adverse events, regardless of severity or relationship to study medication, were recorded on the appropriate CRF as follows: the description of event, date of onset, date event ended, severity, evaluation of drug relationship, and ultimate outcome.

Adverse events were coded using the MedDRA (Medical Dictionary for Regulatory Activities, Version 7.1).

Non-serious adverse events were collected from the time informed consent was signed until study completion. Any AEs reported by the subject to the Investigator after the last scheduled study visit or contact that were considered to be reasonably associated with the use of the study drug were also collected in the appropriate case report form (CRF).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor provided a thesaurus for the coding of all adverse events in the safety database. This listing was examined to assess the adequacy of coding. No important deficiencies were found.

7.1.5.3 Incidence of common adverse events

Table 7.1.5.3.1 enumerates the incidence of treatment-emergent adverse events that occurred in 2% or more of patients in Study 301. >2% TEAEs with a greater incidence in NRP104 patients than in placebo patients were the following: ventricular hypertrophy, upper abdominal pain, dry mouth, nausea, vomiting, pyrexia, hypersensitivity, viral gastroenteritis, scratch, decreased weight, anorexia, decreased appetite, dizziness, headache, psychomotor hyperactivity, sedation, somnolence, affect lability, aggression, agitation, initial insomnia, insomnia, irritability, altered mood, obsessive-compulsive disorder, tearfulness, tic, pharyngolaryngeal pain, pruritis, and rash.

TABLE 7.1.5.3.1: TREATMENT-EMERGENT ADVERSE EVENTS WITH >2% SUBJECTS REPORTING BY PREFERRED TERMINOLOGY, RANDOMIZED POPULATION[14] (STUDY 301)

Preferred Terminology (MedDRA 7.1)	30 mg (n=71) N (%)	30 mg (n=71) AE #	50 mg (n=74) N (%)	50 mg (n=74) AE #	70 mg (n=73) N (%)	70 mg (n=73) AE #	Placebo (n=72) N (%)	Placebo (n=72) AE #	Active Doses (n=218) N (%)	Active Doses (n=218) AE #
Any Events	51 (71.8)	151	50 (67.6)	133	61 (83.6)	202	34 (47.2)	66	162 (74.3)	486
Cardiac disorders	1 (1.4)	1	3 (4.1)	3	1 (1.4)	1	2 (2.8)	2	5 (2.3)	5
Ventricular hypertrophy	0	0	2 (2.7)	2	1 (1.4)	1	0	0	3 (1.4)	3
Eye disorders	1 (1.4)	1	4 (5.4)	4	1 (1.4)	1	0	0	6 (2.8)	6
Gastrointestinal disorders	18 (25.4)	27	12 (16.2)	17	28 (38.4)	43	10 (13.9)	14	58 (26.6)	87
Abdominal pain upper	10 (14.1)	11	5 (6.8)	5	11 (15.1)	12	4 (5.6)	4	26 (11.9)	28
Diarrhoea	1 (1.4)	1	0	0	0	0	2 (2.8)	3	1 (0.5)	1
Dry mouth	2 (2.8)	2	2 (2.7)	2	6 (8.2)	6	0	0	10 (4.6)	10
Nausea	3 (4.2)	3	2 (2.7)	2	8 (11.0)	9	2 (2.8)	2	13 (6.0)	14
Stomach discomfort	1 (1.4)	1	0	0	0	0	2 (2.8)	2	1 (0.5)	1
Vomiting	5 (7.0)	5	4 (5.4)	5	10 (13.7)	13	3 (4.2)	3	19 (8.7)	23
General disorders and administration site conditions	6 (8.5)	6	1 (1.4)	1	4 (5.5)	4	3 (4.2)	3	11 (5.0)	11
Pyrexia	3 (4.2)	3	0	0	2 (2.7)	2	1 (1.4)	1	5 (2.3)	5
Immune system disorders	0	0	2 (2.7)	2	0	0	0	0	2 (0.9)	2
Hypersensitivity	0	0	2 (2.7)	2	0	0	0	0	2 (0.9)	2
Infections and infestations	9 (12.7)	11	13 (17.6)	14	9 (12.3)	10	14 (19.4)	14	31 (14.2)	35
Gastroenteritis viral	1 (1.4)	1	2 (2.7)	2	1 (1.4)	1	0	0	4 (1.8)	4
Influenza	1 (1.4)	1	2 (2.7)	2	0	0	2 (2.8)	2	3 (1.4)	3
Nasopharyngitis	4 (5.6)	4	3 (4.1)	3	4 (5.5)	4	4 (5.6)	4	11 (5.0)	11
Pharyngitis streptococcal	1 (1.4)	1	0	0	0	0	3 (4.2)	3	1 (0.5)	1
Upper respiratory tract infection	3 (4.2)	4	2 (2.7)	2	2 (2.7)	2	3 (4.2)	3	7 (3.2)	8
Injury, poisoning and procedural complications	1 (1.4)	1	2 (2.7)	2	2 (2.7)	2	3 (4.2)	3	5 (2.3)	5
Scratch	1 (1.4)	1	0	0	2 (2.7)	2	0	0	3 (1.4)	3
Investigations	5 (7.0)	5	2 (2.7)	2	14 (19.2)	14	2 (2.8)	2	21 (9.6)	21
Weight decreased	4 (5.6)	4	2 (2.7)	2	14 (19.2)	14	1 (1.4)	1	20 (9.2)	20

Program: T41_034.sas

[14] Defined as subjects who were randomized to and received blind investigational product

Preferred Terminology (MedDRA 7.1)	30 mg (n=71) N (%)	30 mg (n=71) AE #	50 mg (n=74) N (%)	50 mg (n=74) AE #	70 mg (n=73) N (%)	70 mg (n=73) AE #	Placebo (n=72) N (%)	Placebo (n=72) AE #	Active Doses (n=218) N (%)	Active Doses (n=218) AE #
Metabolism and nutrition disorders	27 (38.0)	27	26 (35.1)	27	37 (50.7)	42	4 (5.6)	4	90 (41.3)	96
Anorexia	1 (1.4)	1	3 (4.1)	3	0	0	0	0	4 (1.8)	4
Decreased appetite	26 (36.6)	26	23 (31.1)	24	36 (49.3)	40	3 (4.2)	3	85 (39.0)	90
Musculoskeletal and connective tissue disorders	0	0	1 (1.4)	1	2 (2.7)	2	0	0	3 (1.4)	3
Nervous system disorders	14 (19.7)	15	12 (16.2)	14	21 (28.8)	25	8 (11.1)	9	47 (21.6)	54
Dizziness	5 (7.0)	5	4 (5.4)	4	2 (2.7)	2	0	0	11 (5.0)	11
Headache	7 (9.9)	8	7 (9.5)	8	12 (16.4)	14	7 (9.7)	8	26 (11.9)	30
Psychomotor hyperactivity	0	0	1 (1.4)	1	2 (2.7)	2	0	0	3 (1.4)	3
Sedation	0	0	0	0	2 (2.7)	2	0	0	2 (0.9)	2
Somnolence	2 (2.8)	2	0	0	3 (4.1)	3	1 (1.4)	1	5 (2.3)	5
Psychiatric disorders	25 (35.2)	45	25 (33.8)	35	28 (38.4)	50	2 (2.8)	2	78 (35.8)	130
Affect lability	2 (2.8)	2	2 (2.7)	2	3 (4.1)	3	0	0	7 (3.2)	7
Aggression	2 (2.8)	2	0	0	1 (1.4)	1	0	0	3 (1.4)	3
Agitation	0	0	2 (2.7)	2	1 (1.4)	1	0	0	3 (1.4)	3
Initial insomnia	3 (4.2)	3	2 (2.7)	2	4 (5.5)	4	0	0	9 (4.1)	9
Insomnia	11 (15.5)	16	12 (16.2)	13	18 (24.7)	21	2 (2.8)	2	41 (18.8)	50
Irritability	8 (11.3)	9	6 (8.1)	7	7 (9.6)	8	0	0	21 (9.6)	24
Mood altered	2 (2.8)	2	2 (2.7)	2	0	0	0	0	4 (1.8)	4
Obsessive-compulsive disorder	2 (2.8)	3	0	0	1 (1.4)	1	0	0	3 (1.4)	4
Tearfulness	3 (4.2)	4	1 (1.4)	2	0	0	0	0	4 (1.8)	6
Tic	1 (1.4)	1	1 (1.4)	1	3 (4.1)	3	0	0	5 (2.3)	5
Respiratory, thoracic and mediastinal disorders	8 (11.3)	10	5 (6.8)	5	3 (4.1)	3	8 (11.1)	12	16 (7.3)	18
Cough	2 (2.8)	2	1 (1.4)	1	0	0	4 (5.6)	4	3 (1.4)	3
Nasal congestion	3 (4.2)	3	0	0	0	0	4 (5.6)	4	3 (1.4)	3
Pharyngolaryngeal pain	1 (1.4)	1	2 (2.7)	2	3 (4.1)	3	2 (2.8)	2	6 (2.8)	6
Skin and subcutaneous tissue disorders	1 (1.4)	1	5 (6.8)	6	3 (4.1)	3	1 (1.4)	1	9 (4.1)	10
Pruritus	1 (1.4)	1	2 (2.7)	2	0	0	0	0	3 (1.4)	3
Rash	0	0	3 (4.1)	3	3 (4.1)	3	0	0	6 (2.8)	6

Program: T41_034.sas

7.1.5.4 Common adverse event tables

Please see Section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Adverse events that are considered common and drug-related (i.e., reported in at least 5% of the NRP104 patients at a rate at least twice that in the placebo group) are: upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

7.1.5.6 Additional analyses and explorations

Demographic Effects on Adverse Event Incidence
The sponsor did not perform subgroup analyses of demographic variables (age 6-9 or 10-12, gender, and race white or nonwhite) on the reporting rates of the above common, drug related events.

Dose-Relatedness
The sponsor evaluated the relationship between dose and the reporting incidence of treatment-emergent adverse events. Events examined were those reported by at least 5% of NRP104 patients in any dose group or in all subjects treated with NRP104. Dose groups were: 30 mg (N=71), 50 mg (N=74), and 70 mg (N=73).

There appears to be a dose-related trend for treatment-emergent adverse events of vomiting, nausea, dry mouth, decreased appetite, decreased weight, headache, and insomnia. For all other adverse events there does not appear to be a dose response or it is unclear.

7.1.6 Less Common Adverse Events

I reviewed tables of all adverse events in studies 201[15] and 301[16] and did not find any adverse events that were considered serious adverse events but not already classified as serious.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine hematology, chemistry, and urinalysis testing was done at screening and at final study (or early termination) visit for Study 301.

7.1.7.2 Standard analyses and explorations of laboratory data

7.1.7.2.1 Analyses focused on measures of central tendency

Mean Change from Baseline in Laboratory Tests
Mean changes from baseline were computed for several laboratory variables[17] for Study 301. Results are displayed in Table 8.2.1 of the CSR for Study 301.

For Study 301, mean changes from baseline to final visit assessment were statistically significantly different between NRP and placebo for eosinophils, Hct, Hgb, lymphocytes, neutrophils, RBC, albumin, alkaline phosphatase, BUN, calcium, and ALT. Data are presented in Table 7.1.7.2.1.1 below.[18]

[15] Table 4.1.3 of the CSR for Study 201
[16] Table 4.1.3 of the CSR for Study 301
[17] Basophils, eosinophils, Hct, Hgb, lymphocytes, MCH, MCH concentration, MCV, monocytes, neutrophils, platelet count, RBC, WBC, albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose, GTT, potassium, sodium, phosphorus, total protein, AST, ALT, TSH, uric acid, urine pH, and urine specific gravity
[18] Changes for other variables were not significantly different between drug and placebo.

TABLE 7.1.7.2.1.1: LABORATORY PARAMETERS WITH DIFFERENCES AMONG TREATMENTS (P<0.05) IN MEAN CHANGE FROM BASELINE TO ENDPOINT FOR THE RANDOMIZED POPULATION[19] (STUDY 301)

Parameters	Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg	P value‡
Hematology:					
Eosinophils (%)	0.14	-0.51	-0.61	-1.13	0.0127
Hematocrit (HCT) (%)	-0.50	0.27	0.63	0.71	0.0020
Hemoglobin (HGB) (g/dL)	-0.16	0.16	0.29	0.30	0.0001
Lymphocytes (%)	3.28	-1.48	-1.09	-2.60	0.0396
Neutrophils (%)	-4.50	1.40	1.13	3.90	0.0078
RBC (m/uL)	-0.04	0.08	0.12	0.14	<.0001
Clinical Chemistry:					
Albumin (g/dL)	-0.20	-0.10	0.00	-0.05	0.0003
Alkaline Phosphatase (IU/L)	-2.10	-24.09	-14.57	-26.25	0.0110
BUN (mg/dL)	-0.25	-1.98	-0.88	-1.96	0.0249
Calcium (mg/dL)	-0.08	-0.01	0.02	0.09	0.0057
SGPT (ALT) (IU/L)	1.96	-2.16	-2.03	-0.72	0.0097

‡ P value by ANCOVA with screening as covariate
Source: Section 15 Tables 8.1.1 to 8.1.3.

The mean changes in eosinophils, Hct, Hgb, lymphocytes, neutrophils, RBC, albumin, BUN, calcium, and ALT were small and unlikely to be clinically significant. The mean change in alkaline phosphatase was large, though its clinical significance is unclear.

7.1.7.2.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Laboratory Changes
Criteria for potentially clinically important (PCI) laboratory test results are displayed in Appendix 10.5.2 in Section 10.5. The proportions of patients who met these criteria for Study 301 were extracted from the sponsor's 6/28/06 submission and are displayed in Appendix 10.5.3 in Section 10.5. Of note, there are several problems with the sponsor's presentation of the data. It is not broken down by dose group, and the outlier criteria for LDH and creatine kinase are missing.

The proportions were comparable between the NRP104 group and placebo group for most laboratory parameters in Study 301. For a non-negative protein urinalysis result, proportions were 20% (43/218) in the NRP104 group and 10% (7/72) in the placebo group. The difference was not statistically significant (chi-square=3.795, p=0.051). For a non-negative ketones

[19] Defined as subjects who were randomized to and received blind investigational product

urinalysis result, proportions were 6% (13/218) in the NRP104 group and 0% (0/72) in the placebo group. The difference was not statistically significant (chi-square with Yate's continuity correction=3.2102, p=0.073).

7.1.7.2.3 Marked outliers and dropouts for laboratory abnormalities

Dropouts due to Laboratory Abnormalities
No NRP patients in the Study 301 dropped out due to laboratory abnormalities.

7.1.7.3 Additional analyses and explorations

No laboratory parameters warranted additional exploration.

7.1.7.4 Special assessments

The above analyses revealed no evidence of any particular toxicity manifested as a laboratory test abnormality.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital Sign Assessments
For Study 301, pulse, systolic and diastolic blood pressure, and body temperature were measured at screening, baseline, at each post-baseline weekly visit, and at endpoint.

Weight and Height Assessments
For Study 301, weight and height were measured at screening and at endpoint.[20]

[20] Of note, the sponsor did not provide a description of height and weight measurement methodology. This information was requested in a 7/17/06 email.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Mean Change from Baseline in Vital Sign Measures
For Study 301, the mean changes from baseline to various study visits in pulse, systolic and diastolic blood pressure, and body temperature are displayed by visit in Tables 5.1.1 to 5.1.4 of the Clinical Study Report for Study 301. Mean changes from baseline to final on-therapy assessment were statistically different between NRP104 and placebo for pulse. Data are presented in Table 7.1.8.3.1.1 below.

TABLE 7.1.8.3.1.1: MEAN CHANGES FROM BASELINE IN BLOOD PRESSURE, PULSE, AND TEMPERATURE (STUDY 301): RANDOMIZED POPULATION[21]

Visit	Statistics	Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg	P value‡
Pulse (bpm)						
Baseline	Mean (SD)	80.8 (8.73)	82.2 (9.78)	81.7 (11.46)	82.8 (12.20)	0.7211
Endpoint	Mean (SD)	80.8 (9.97)	82.3 (10.69)	83.8 (10.81)	86.3 (11.39)	
	Change† (SE)	-0.7 (1.17)	0.3 (1.20)	2.0 (1.18)	4.1 (1.17)	0.0224*
Systolic Blood Pressure (mmHg)						
Baseline	Mean (SD)	102.4 (9.35)	103.9 (10.86)	103.3 (9.67)	101.9 (8.82)	0.6122
Endpoint	Mean (SD)	103.9 (10.14)	103.9 (11.47)	104.8 (10.79)	105.0 (8.31)	
	Change† (SE)	1.3 (1.05)	0.4 (1.08)	1.8 (1.06)	2.6 (1.05)	0.5241
Diastolic Blood Pressure (mmHg)						
Baseline	Mean (SD)	64.4 (7.07)	64.3 (6.56)	64.6 (7.22)	63.9 (7.50)	0.9439
Endpoint	Mean (SD)	64.9 (8.94)	64.9 (7.97)	66.3 (8.37)	66.5 (7.88)	
	Change† (SE)	0.6 (0.91)	0.6 (0.93)	1.9 (0.92)	2.3 (0.91)	0.4245
Body Temperature (F)						
Baseline	Mean (SD)	98.0 (0.77)	98.1 (0.76)	98.1 (0.91)	98.0 (0.74)	0.7212
Endpoint	Mean (SD)	98.1 (0.76)	98.1 (0.86)	98.1 (0.87)	98.1 (0.89)	
	Change† (SE)	0.0 (0.10)	-0.0 (0.10)	-0.0 (0.10)	0.1 (0.09)	0.8312

* Indicates statistical significance p<0.05
† LS mean change from baseline to endpoint where endpoint was the last valid observation post baseline.
‡ P value by ANCOVA (ANOVA for baseline)
Source: Section 15 Tables 5.1.1 to 5.1.4.

[21] Defined as subjects who were randomized to and received blind investigational product

The mean change in pulse was small and unlikely to be clinically significant, and modest increases in average heart rate are noted in the WARNINGS section of standard stimulant labeling.

Mean Change from Baseline in Weight and Height Measures
For Study 301, the mean changes from baseline to final on-therapy assessment were statistically different between NRP104 and placebo for weight. Of note, adjustments for age and sex were not made.[22] Data are presented in Table 7.1.8.3.1.2 below.

TABLE 7.1.8.3.1.2: MEAN CHANGES FROM BASELINE IN WEIGHT AND HEIGHT (STUDY 301): RANDOMIZED POPULATION[23]

Visit	Statistics	Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg	P value‡
Body Weight (lb)						
Baseline	Mean (SD)	82.6 (22.82)	80.9 (27.25)	80.7 (25.39)	79.0 (23.70)	0.8644
Endpoint	Mean (SD)	82.8 (22.85)	80.9 (28.48)	78.8 (25.67)	74.9 (20.09)	
	Change† (SE)	1.0 (0.37)	-0.9 (0.38)	-1.9 (0.37)	-2.5 (0.37)	<.0001 *
Height (in)						
Baseline	Mean (SD)	55.0 (3.88)	54.3 (4.75)	53.8 (4.12)	53.7 (4.09)	0.2399
Endpoint	Mean (SD)	55.1 (3.87)	54.5 (4.81)	53.8 (4.16)	53.7 (4.20)	
	Change† (SE)	0.2 (0.06)	0.2 (0.06)	0.2 (0.06)	0.2 (0.06)	0.8781

* Indicates statistical significance p<0.05
† LS mean change from baseline to endpoint where endpoint was the last valid observation post baseline.
‡ P value by ANCOVA (ANOVA for baseline)
Source: Section 15 Tables 7.2.1 to 7.2.2.

The mean change in weight was large. However, without adjustment for age and sex, this data is difficult to interpret.

Study 302 was ongoing as of the data cut-off date. The sponsor has not submitted a Final Clinical Study Report at the time of completion of this review. The weight and height data from Study 302 will be reviewed in an addendum when the sponsor submits the Clinical Study Report for this study.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant Vital Sign Changes

[22] This information was requested in a 7/17/06 email.
[23] Defined as subjects who were randomized to and received blind investigational product

Criteria for potentially clinically important (PCI) vital sign results are displayed in Appendix 10.5.4 in Section 10.5. The proportions of patients who met these criteria for Study 301 were extracted from the sponsor's 6/28/06 submission and are displayed in Appendix 10.5.5 in Section 10.5.

There were no PCI changes among NRP104 patients that were at least 5% and twice that among placebo patients.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

Dropouts due to Vital Sign or Weight and Height Abnormalities
In Study 301, the proportions of patients who experienced a change in vital signs or weight that led to premature discontinuation are displayed in Table 7.1.8.3.3.1 below. The incidences for dropout due to weight loss and due to hypertension were higher in the NRP104 70 mg group than in the placebo group. The difference was not statistically significant (p=1, 2-tailed Fishers exact test). In the patient who dropped out due to weight loss, the decrease from baseline (57.0 lb) was 4.6 pounds. In the patient who dropped out due to hypertension, the maximum increase from baseline was 11 mm Hg for diastolic blood pressure, and 17 mm Hg for systolic blood pressure.

TABLE 7.1.8.3.3.1: DROPOUTS DUE TO VITAL SIGN OR WEIGHT AND HEIGHT CHANGES (STUDY 301): RANDOMIZED POPULATION[24]

Abnormality	NRP104 30 mg (N=71)	NRP104 50 mg (N=74)	NRP104 70 mg (N=73)	PLACEBO (N=72)
Weight loss	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)
Hypertension	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)

7.1.8.4 Additional analyses and explorations

No further explorations were deemed necessary.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG Assessments
For Study 301, standard 12-lead electrocardiograms were performed at screening, baseline, at each post-baseline weekly visit, and at endpoint. At screening, at least 3 ECG tracings were

[24] Defined as subjects who were randomized to and received blind investigational product

taken at least 10 minutes apart. QTc was corrected for heart rate using both Fridericia's and Bazett's formula.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

Mean Change from Baseline in ECG parameters
For Study 301, mean changes from baseline to final on-therapy assessment were computed for the NRP104 and placebo treatment groups. Results are displayed in Table 27 of the CSR for Study 301.

For Study 301, mean changes from baseline to final on-therapy assessment were statistically significantly different between NRP104 and placebo for heart rate, RR interval, and QRS interval. Data are presented in Tables 7.1.9.3.1.1 below. [25]

TABLE 7.1.9.3.1.1: CHANGE IN ECG PARAMETERS FROM BASELINE TO ENDPOINT (STUDY 301): RANDOMIZED POPULATION[26]

	Placebo		NRP104 30 mg		NRP104 50 mg		NRP104 70 mg		p-value
	N	Mean Δ	N	Mean Δ	N	Mean Δ	N	Mean Δ	
Heart rate (beats/ min)	71	-0.9	69	2.1	71	2.2	72	3.5	≤ 0.05
RR interval (ms)	71	10.2	69	-16.8	71	-20.5	72	-32.2	≤ 0.05
QRS interval (ms)	71	-0.6	69	0.7	71	0.7	72	2.1	≤ 0.05

The changes in heart rate and QRS interval were generally small and unlikely to be clinically significant. Modest increases in average heart rate are noted in the WARNINGS section of standard stimulant labeling. Though the drug/placebo difference in RR interval was 42.2 msec, it is likely related to clinically insignificant increases in heart rate.

[25] Changes for other variables were not significantly different between drug and placebo.
[26] Defined as subjects who were randomized to and received blind investigational product

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

Potentially Clinically Significant ECG Changes
Criteria for potentially clinically important (PCI) laboratory test results are displayed in Appendix 10.5.6 in Section 10.5. The proportions of patients who met these criteria for Study 301 were extracted from the sponsor's 6/28/06 submission and are displayed in Appendix 10.5.7 in Section 10.5.

There were no PCI changes among NRP104 patients that were at least 5% and twice that among placebo patients.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

Dropouts due to ECG Abnormalities
In Study 301, the proportions of patients who experienced an ECG abnormality that led to premature discontinuation are displayed in Table 7.1.9.3.3.1 below. The incidence for dropout due to QRS voltage criteria for left ventricular hypertrophy was higher in the NRP104 50 mg and 70 mg groups than in the placebo group. The differences were not statistically significant (p=1, 2-tailed Fishers exact test).

TABLE 7.1.9.3.3.1: DROPOUTS DUE TO ECG ABNORMALITIES (STUDY 301): RANDOMIZED POPULATION[27]

Abnormality	NRP104 30 mg (N=71)	NRP104 50 mg (N=74)	NRP104 70 mg (N=73)	PLACEBO (N=72)
QRS voltage criteria for left ventricular hypertrophy	0 (0%)	1 (1.4%)	1 (1.4%)	0 (0%)

7.1.9.4 Additional analyses and explorations

No ECG parameters warranted additional exploration.

7.1.10 Withdrawal Phenomena and/or Abuse Potential

According to a 5/4/06 email from Katherine Bonson, Ph.D., of the Controlled Substances Staff (CSS), [redacted] will be recommending Schedule II. Neither her consultation results nor a draft of these results was available the time of completion of this review.

[27] Defined as subjects who were randomized to and received blind investigational product

7.1.11 Human Reproduction and Pregnancy Data

There were no studies in this submission designed specifically to assess safety in human reproduction and pregnancy. No human reproduction was available. A review of serious adverse events revealed no pregnancies during the NRP104 studies.

7.1.12 Assessment of Effect on Growth

See Section 7.1.8.3.

The sponsor did not provide outlier analyses for height and weight or a description of height and weight measurement methodology.[28]

7.1.13 Overdose Experience

There was no overdosage experience with NRP104 in humans. No cases of accidental or intentional overdose with NRP104 were reported.

7.1.14 Postmarketing Experience

NRP104 has not been marketed.

[28] This information was requested in a 7/17/06 email.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

TABLE 7.2.1.1.1: NRP104 STUDIES, INCLUDING SAFETY POPULATION ENUMERATION

Phase I Studies	
Single-Dose	
102	Open-label, 3-treatment, 3-period, 6-sequence, randomized, crossover study to assess the relative bioavailability of d-amphetamine of NRP104 70 mg in 18 healthy subjects aged 18 to 55 when administered orally under 3 dosing conditions: an intact capsule only, a solution containing the capsule contents, and an intact capsule with high fat meal. Safety population consisted of 18 subjects.
101	Open-label, randomized, two-period crossover study to compare the rate of absorption and oral bioavailability of two dose levels (25 and 75 mg) of NRP 104 test formulation to oral doses of Dexedrine 30 mg and Adderall XR 35 mg in 20 healthy subjects aged 18 to 55. Safety population consisted of 20 subjects.
106	Open-label study to assess the distribution, metabolism, and elimination of NRP-104 radiolabel with ^{14}C in 6 healthy subjects aged 18 to 55. Safety population consisted of 6 subjects.
103	Open-label, 3-treatment, 3-period, 6 sequence, randomized, crossover study to asses dose proportionality of d-amphetamine after oral administration of 30, 50, and 70 mg of NRP104 after an overnight fast in 18 children with ADHD aged 6 to 12. Safety population consisted of 18 patients.
Multiple-Dose	
104	Open-label study to assess steady state pharmacokinetics of NRP104 70 mg following 7-day once-daily administration in fasting 12 healthy subjects aged 18 to 55. Safety population consisted of 12 subjects.
Completed Phase 2/3 Studies	
201	Multi-center, randomized, double-blind, 3-treatment, 3-period (one week each) crossover study following an 3-week, open-label Adderall XR titration period to assess, in a controlled environment, the efficacy and safety of NRP104 (30, 50, or 70 mg) and Adderall XR (10, 20, or 30 mg) compared to placebo in 52 children with ADHD aged 6 to 12. Safety population consisted of 50 patients treated with NRP104. Three of these subjects had prior treatment with NRP104

	in a Phase I study.
301	Multi-center, randomized, double-blind, placebo-controlled, parallel-group fixed-dose, 4 week study to assess the efficacy and safety of NRP104 (30, 50, or 70 mg) compared to placebo in 297 children with ADHD aged 6 to 12. The sponsor defined the safety population as all enrolled patients (297). However, safety analyses were performed using the randomized population, which was defined as all subjects who received blind investigational product and consisted of 72 patients assigned to placebo and 218 patients assigned to NRP104.
Ongoing Phase 2/3 Study	
302	Multi-center, open-label, and single-arm study to assess the safety of NRP104 (30, 50, or 70 mg) for up to one year in children with ADHD aged 6 to 12. As of the NDA submission, 273 patients have been enrolled. Safety population consisted of 271 patients, of which 209 had prior treatment with NRP104 in either Study 301 or 201.
Abuse Studies	
A01	Single-center, single-blind, 2 month study to determine the safety and tolerability of increasing single oral doses of NRP104 (up to 150 mg) compared to placebo and d-amphetamine sulfate 40 mg and to gather preliminary estimates of abuse liability in 12 subjects with a history of stimulant abuse aged 18 to 55.
A02	Single-center, double-blind, randomized study to determine the safety, tolerability, and abuse liability of single intravenous doses of NRP104 25 and 50 mg compared to placebo and d-amphetamine sulfate in 12 subjects with a history of stimulant abuse aged 18 to 55.
A03	Single-center, double-blind, randomized, placebo-controlled, six-period crossover study to determine whether the abuse potential of NRP104 (50, 100, and 150 mg) is less than that of immediate release d-amphetamine sulfate 40 mg and diethylpropion hydrochloride 200 mg in 36 patients with a diagnosis of stimulant abuse aged 18 to 55.

7.2.1.2 Demographics

TABLE 7.2.1.2.1 : STUDY 301[29]
BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION[30]

TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
NRP104 30 mg (71)	9.0	6-12	75	25	52	25	14	6
NRP104 50 mg (74)	8.9	6-12	62	38	46	26	23	4
NRP104 70 mg (73)	8.7	6-12	71	29	56	23	16	3
Placebo (72)	9.4	6-12	69	31	60	22	12	4

TABLE 7.2.1.2.1 : PHASE 1 STUDIES[31]
BASELINE DEMOGRAPHICS, SAFETY POPULATION

TX (n)	Age (yrs)		Sex (%)		Race (%)		
	Mean	Range	Male	Female	White	Black	Other
NRP104 Children (18)	9.6	6-12	56	44	44	44	11
NRP104 Adults (56)	33.5	18-52	54	46	66	20	14

[29] Figures may not add up to 100% due to rounding.
[30] Defined as subjects who were randomized to and received blind investigational product
[31] Figures may not add up to 100% due to rounding.

TABLE 7.2.1.2.2 : PHASE 2-3 STUDIES[32] BASELINE DEMOGRAPHICS, SAFETY POPULATION							
TX	**Age (yrs)**		**Sex (%)**		**Race (%)**		
(n)	Mean	Range	Male	Female	White	Black	Other
NRP104 Short-Term (268)	8.9	6-12	68	32	60	25	15
Placebo Short-Term (124)	9.3	6-12	67	33	62	23	15
NRP104 Long-Term (271)	9.2	6-13	69	31	59	26	14

7.2.1.3 Extent of exposure (dose/duration)

The sponsor provided tables presenting the overall exposure for Phase 1 single-dose, Phase 1 multiple dose, and Phase 2-3 studies, respectively. These tables are extracted from the sponsor's submission and included below.

[32] Figures may not add up to 100% due to rounding.

TABLE 7.2.1.3.1: NUMBER OF SUBJECTS DOSED AND NUMBER OF DOSES ADMINISTERED IN PHASE 1 SINGLE-DOSE STUDIES

Medication	Study	Formulation: Capsules						
		25 mg (1x25mg) N (counts)	30 mg (1x30mg) N (counts)	35 mg (1x30mg & 1x5mg) N (counts)	50 mg (1x50mg) N (counts)	70 mg (1x70mg) N (counts)	75 mg (3x25mg) N (counts)	Any Dose [1] N (counts)
NRP104	NRP104.101	10 (10)					10 (10)	20 (20)
	NRP104.102					18 (54)		18 (54)
	NRP104.103 (pediatric)		18 (18)		17 (17)	17 (17)		18 (53)
	NRP104.106					6 (6)		6 (6)
	All studies	10 (10)	18 (18)		17 (17)	41 (77)	10 (10)	62 (133)
Adderall XR	NRP104.101			10 (10)				10 (10)
Dexedrine	NRP104.101		10 (10)					10 (10)

[1] Subjects who crossed over to an alternate treatment(s) of the same medication were counted only once.

TABLE 7.2.1.3.2: NUMBER (%) OF SUBJECTS DOSED IN PHASE I MULTIPLE DOSES STUDY

Medication	*Study No.*	*Duration*	Formulation: Capsules			
			30 mg	50 mg	70 mg	Any Dose
NRP104	NRP104.104	1 day	-	-	1 (8%)	1 (8%)
		7 days	-	-	11 (92%)	11 (92%)
		Total	-	-	12	12

TABLE 7.2.1.3.3: NUMBER (%) OF SUBJECTS EXPOSED TO ACTIVE STUDY MEDICATION BY DAILY DOSE AND TREATMENT IN PHASE 2-3 STUDIES

Study Number	Duration of Exposure (weeks)	NRP104 (Actual Dose) 30mg	50mg	70mg	Any Dose [1]	Adderall XR (10-30mg)
NRP104.201	1	8 (100.0)	17 (100.0)	25 (100.0)	50 (100.0)	
	3					1 (1.9)
	4+					51 (98.1)
	Total No. of Subjects	8	17	25	50	52
NRP104.301	1	100 (45.9)	64 (46.7)	3 (4.6)	11 (5.0)	
	2	54 (24.8)	12 (8.8)	43 (66.2)	13 (6.0)	
	3	6 (2.8)	45 (32.8)	19 (29.2)	13 (6.0)	
	4+	58 (26.6)	16 (11.7)		181 (83.0)	
	Total No. of Subjects	218	137	65	218	
NRP104.302	01-04	182 (67.4)	88 (40.0)	26 (21.7)	18 (6.6)	
	05-08	20 (7.4)	36 (16.4)	17 (14.2)	13 (4.8)	
	09-12	17 (6.3)	24 (10.9)	20 (16.7)	14 (5.2)	
	13-16	16 (5.9)	26 (11.8)	19 (15.8)	44 (16.2)	
	17-20	13 (4.8)	24 (10.9)	16 (13.3)	69 (25.5)	
	21-24	12 (4.4)	13 (5.9)	13 (10.8)	60 (22.1)	
	25-32	9 (3.3)	9 (4.1)	9 (7.5)	51 (18.8)	
	33-48	1 (0.4)			2 (0.7)	
	Total No. of Subjects	270	220	120	271	
Short-Term Studies (201/301)	1	108 (47.8)	81 (52.6)	28 (31.1)	61 (22.8)	
	2	54 (23.9)	12 (7.8)	43 (47.8)	13 (4.9)	
	3	6 (2.7)	45 (29.2)	19 (21.1)	13 (4.9)	1 (1.9)
	4+	58 (25.7)	16 (10.4)		181 (67.5)	51 (98.1)
	Total No. of Subjects	226	154	90	268	52
TOTAL (201/301/302)	01-04	194 (60.8)	124 (47.1)	72 (43.4)	62 (18.8)	29 (55.8)
	05-08	50 (15.7)	35 (13.3)	13 (7.8)	19 (5.8)	23 (44.2)
	09-12	17 (5.3)	23 (8.7)	21 (12.7)	15 (4.5)	
	13-16	18 (5.6)	29 (11.0)	18 (10.8)	21 (6.4)	
	17-20	15 (4.7)	28 (10.6)	19 (11.4)	43 (13.0)	
	21-24	9 (2.8)	12 (4.6)	12 (7.2)	72 (21.8)	
	25-32	15 (4.7)	12 (4.6)	11 (6.6)	95 (28.8)	
	33-48	1 (0.3)			3 (0.9)	
	Total No. of Subjects	319	263	166	330	52

[1] Subjects who received the different daily doses were counted only once
Program: T05_03.sas

A total of 98 patients (30% of all 330 patients) had an exposure to NRP104 of over 25 weeks. Eleven of these 98 patients received a daily dose of 70 mg/day. One hundred sixty six patients (50%) of all 330 patients received a mean dose of 70 mg/day.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Due to study design, studies 102, 101, 104, 106, 103, 201, 302, A01, A02, and A03 were not included in the primary safety database.

7.2.2.2 Postmarketing experience

NRP104 has not been marketed.

7.2.2.3 Literature

A literature search was not performed, though it was requested in a 3/1/06 Agency email.

7.2.3 Adequacy of Overall Clinical Experience

Upon submission of the Final Clinical Study Report for study 302, overall clinical experience will be adequate, if safety data is acceptable.

7.2.4 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

A Clinical Pharmacology and Biopharmaceutics review was not available at the time of completion of this review.

7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further study.

7.2.7 Assessment of Quality and Completeness of Data

An audit of the Case Report Forms (CRF's), Narrative Summaries, and adverse event data listings was conducted for 2 patients whom I randomly selected from the database for this supplement (10% of the 22 patients with submitted CRF's).[33] The adverse event data listings examined were in M5 V81 (page 679) and in M5 V83 (page 2044). No Narrative Summaries were provided.

An examination of the adverse event information across these sources for each of the 2 patients revealed reasonable consistency and completeness.

In addition, the Division of Scientific Investigations (DSI) inspected two sites from studies 201 and 301 and one site from Study 301. The results of these inspections are presented in Section 3.4 above. Overall, the data from one of the sites appeared to be acceptable for use in support of this NDA supplement, but data from the remaining 2 sites is still pending.

7.2.8 Additional Submissions, Including Safety Update

Study 302 was ongoing as of the data cut-off date (January 16, 2006) for the 4-Month Safety Update. Thus, the safety information for study 302 was derived from near-completion and primary-safety-audited data available as of the cut-off date. This review includes the clinical data contained in the 4-Month Safety Update.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

This submission revealed only findings consistent with the previously observed safety profile of amphetamines.

7.4 General Methodology

7.4.1 Pooling Data across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Due to differences in study design, studies were not pooled.

[33] This consisted of 1 patient from Study 201 (201/03-008) and 1 patient from Study 301 (301/55-313).

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Please see Section 7.1.5.6

7.4.2.2 Explorations for drug-demographic interactions

Please see Section 7.1.5.6.

7.4.2.3 Explorations for drug-disease interactions

There were no studies addressing drug-disease interactions in this submission.

7.4.2.4 Explorations for drug-drug interactions

There were no studies addressing drug-drug interactions in this submission.

7.4.3 Causality Determination

Adverse events were considered common and possibly drug-related if they were reported in at least 5% of the NRP104 patients at a rate at least twice that in the placebo group in Study 301.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 301 was a fixed dose study of NRP104 that examined doses of 30, 50, and 70 mg/day versus placebo in the treatment of attention deficit hyperactivity disorder. All three dose groups produced a significant difference over placebo.

Patients were randomized to 30, 50, and 70 mg treatment groups. For all dose groups, dosing for NRP104 began at 30 mg/day for the first week of treatment. For the 50 and 70 mg treatment groups, dosage was increased to 50 mg/day at week 2. For the 70 mg treatment group, dosage was increased to 70 mg/day at week 3.

Based on drug/placebo comparisons, there was evidence of a significant treatment effect for the low dose ($p<0.0001$), and results at the two higher doses were similar in both robustness ($p<0.0001$) and magnitude of effect size (placebo-adjusted difference of -15.58, -17.21, and -

20.49 for 30 mg, 50 mg, and 70 mg, respectively). The mean change from baseline at endpoint was -21.8 (SE=1.60), -23.4 (SE=1.56), and -26.7 (SE=1.54) for the 30 mg, 50 mg, and 70 mg groups, respectively. The difference between the 30 mg and 70 dose groups could be as small as 0.2 on a 54-point scale, which is unlikely to be clinically significant. Therefore, there appears to be no substantial advantage of the higher doses (50 and 70 mg) over the lower dose (30 mg).

8.2 Drug-Drug Interactions

There were no serious adverse events that suggested drug-drug interactions. There were no drug-drug interaction studies in the submission.

8.3 Special Populations

Please see Section 6.1.4.

8.4 Pediatrics

[redacted]

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drugs Advisory Committee.

8.6 Literature Review

The sponsor did not perform a literature review, despite our 3/1/06 email request.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations.

8.8 Other Relevant Materials

The Division of Drug Marketing, Advertising and Communications (DDMAC) found the sponsor's initially proposed proprietary name, [redacted], unacceptable from a promotional perspective and the Division concurred (ODS consult 06-0041, dated 2/28/06). The sponsor submitted the alternate name, [redacted], which DDMAC found unacceptable from a promotional

perspective, and the Division concurred (ODS consult 06-0041-1, dated 3/23/06). The submission of an alternative proprietary name for this NDA was requested.

9 OVERALL ASSESSMENT

9.1 Conclusions

This submission revealed only safety findings consistent with the previously observed safety profile of amphetamines.

The sponsor has provided evidence from one crossover study (Study 201) and one parallel-group study (Study 301) with three doses of (30, 50, and 70 mg/day) that supports the claim of short-term efficacy for the use of NRP104 in attention deficit hyperactivity disorder.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement be granted approvable status. There are a number of requests[34] to which the sponsor has not yet responded. These responses will be reviewed in an addendum.

In addition, it is recommended that the following be conveyed to the sponsor in the approvable letter:

1. In your laboratory test outlier criteria from your 6/28/06 submission, you neglected to include the outlier criteria for LDH (≥3x ULN) and creatine kinase (≥2x ULN) that was in your 3/16/06 submission. Please perform an outlier analysis for Study 301 using these outlier criteria.
2. Please provide information on withdrawal of your product in other countries and submission of marketing authorization applications to foreign regulatory agencies.
3. Your inclusion criteria included: "meets DSM-IV-TR criteria for a primary diagnosis of ADHD combined type or predominantly hyperactive-impulsive subtype based on a detailed psychiatric evaluation which reviews the DSM-IV-TR

[34] These requests are summarized as follows: 1) literature search, 2) enumeration of adverse events pre-marketing adverse events not reported in the >2% Table for the Safety Populations of Studies 201 and 301, 3) enumeration of ITT population patients using concomitant medications during the double-blind period of Study 201 and during Study 301, 4) enumeration of patients that were identified as protocol violators because of prohibited medication use for Studies 201 and 301, 5) serious adverse event definition, 6) mean change from baseline analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, 7) outlier analyses for height and weight with adjustments for age and sex by converting to z-scores for Study 301, and 8) description of height and weight measurement methodology

criteria". Based on your protocol, it appears that a K-SADS-PL was performed. Was your inclusion criteria based on an ADHD diagnosis on the K-SADS-PL?

4. For Study 301, please perform an interaction analyses on your demographic analyses for efficacy
5. For Study 301, perform a subgroup analyses of demographic variables (age 6-9 or 10-12, gender, and race white or nonwhite) on the reporting rates of the common, drug related events (i.e., reported in at least 5% of the NRP104 patients at a rate at least twice that in the placebo group): upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.
6. Please provide narratives for the cases of neutropenia and chest pain noted in Appendix Table 6.12 of the Summary of Clinical Safety as adverse events associated with treatment discontinuation.
7. According to our calculations based on Appendix Tables 5.1, 5.2, and 5.3 of the Summary of Clinical Safety, total exposures were 404, and included 348 pediatric patients. In the ADVERSE EVENTS section of your proposed labeling, you state, "The development program for [TRADE NAME] included exposures in a total of 414 participants in clinical trials (358 pediatric patients and 56 healthy adult subjects). Of these, 358 pediatric patients…" Please explain this discrepancy.
8. Please replace Table 2 in the ADVERSE EVENTS section of your proposed labeling with a >2% table, reflecting data from Table 4.1.4 on pages 273 and 274 of 4099 of the CSR for Study 301. We would recommend entitling the table "Adverse Events Reported by More Than 2% of Pediatric Patients Receiving [TRADE NAME] with Higher Incidence Than on Placebo in a Clinical Study" and entitling its columns "Body System", "Preferred Term", "[TRADE NAME] (n=218)", and "Placebo (n=72)".
9. Information in the last paragraph of the ADVERSE EVENTS section (beginning with, "The following adverse reactions have been associated…") of your proposed labeling should be updated to reflect your response to Comments 11 and 1 of our 3/1/06 and 7/17/06 email requests, respectively.

Final approval is contingent on satisfactory responses to the concerns conveyed in previous requests for information and in the approvable letter, satisfactory Final Clinical Study Report for Study 302, satisfactory DSI, CSS, Statistical, CMC, Pharm/Tox, and Biopharm reviews, and mutual agreement on labeling (see section 9.4).

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommendations for risk management beyond those already in the sponsor's proposed labeling and in amphetamine labeling. Please see Section 9.4 for further details.

9.3.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments from a clinical perspective.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

[redacted]

7 Page(s) Withheld

Trade Secret / Confidential

✓ Draft Labeling

Deliberative Process

Withheld Track Number: Medical Review-1

10 APPENDICES

10.1 Review of Individual Study Reports

Study 201[36]

Investigators/Sites
Four investigators conducted this study at 4 sites in the U.S. Investigators and sites are listed in the Appendix 10.3.1 in Section 10.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial 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 DSM-IV-TR.

Patient Sample
Important inclusion criteria were:
- age 6 to 12 years, inclusive
- meets DSM-IV-TR criteria for a primary diagnosis of ADHD combined type or predominantly hyperactive-impulsive subtype based on a detailed psychiatric evaluation which reviews the DSM-IV-TR criteria
- stable regimen of stimulants for at least one month in the last 6 months
- adequate response to stimulants based on clinical assessment
- functioning at age-appropriate academic level

The following were relevant exclusion criteria:
- comorbid psychiatric diagnosis by K-SADS-PL that, in the opinion of the examining physician contraindicates Adderall XR or NRP 104 treatment or confounds efficacy or safety assessments
- comorbid illness that could interfere with participation in the study
- history of seizure during the last 2 years (exclusive of febrile seizures), a tic disorder, a current diagnosis and/or family history of Tourette's Disorder
- documented history of aggressive behavior serious enough to preclude participation in regular classroom activities
- use of clonidine or anticonvulsant drugs
- use of medications that affect BP or HR or that have CNS effects or that can affect performance

[36] Note that important protocol changes are incorporated into my description of the protocol.

- concurrent illness, disability, or other condition that might confound the results of safety or efficacy assessments or that might increase risk to the subject or that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. This would include psychosocial factors that could lead to difficulty complying with the protocol.
- history of drug dependence or substance abuse disorder according to DSM-IV-TR criteria (excluding nicotine)
- hyperthyroidism, glaucoma
- pregnancy or lactation

Design
This was a Phase II, multicenter, randomized, double-blind, 3-treatment and 3-period crossover comparison of one fixed dose of NRP 104 and one fixed dose of Adderall XR with placebo in a school laboratory environment. The school laboratory environment included an analog classroom and lasted for a 13-hour school day. Eligible patients entered a 3-week open-label dose titration with Adderall XR, receiving 10 mg/day the first week, 10 or 20 mg/day the second week, and 10, 20, or 30 mg/day the third week. Dosage adjustments were based on investigator evaluation of therapeutic response and tolerability. The Adderall XR dose used in the third titration week was considered the optimal dose of Adderall XR.

After the open-label dose titration with Adderall XR, patients received a 3-way crossover treatment of one week each during which they received either NRP 104, Adderall XR, or placebo in a double-blind and randomized fashion. Patients were dispensed one blister card each week containing identically-appearing capsules that came from either Category A drug kit, Category B drug kit, or Category C drug kit depending upon the optimal dose of Adderall XR achieved during the dose titration period as illustrated in the table below. They were instructed to take one capsule each morning from each row of the blister card they received for the first 6 days. On Day 7 of each double-blind week patients took the Day 7 dose of the treatment at the laboratory school upon arrival. Patients returned for a poststudy evaluation within 3 days following the last laboratory school visit or at the time of early study withdrawal. The table below was extracted from the sponsor's submission.

Drug Kit Category	Number and Type of Investigational Product Capsules Per Blister Card	For Dispensing
A	1 card with one (1) row of nine (9) NRP104 30 mg capsules 1 card with one (1) row of nine (9) Adderall XR® 10 mg capsules 1 card with one (1) row of nine (9) placebo capsules	Subjects whose optimal Adderall XR® dose is 10 mg per day
B	1 card with one (1) row of nine (9) NRP104 50 mg capsules, and one (1) row of nine (9) placebo capsules 1 card with two rows of nine (9) Adderall XR® 10 mg capsules each row 1 card with two (2) rows of nine (9) placebo capsules each row	Subjects whose optimal Adderall XR® dose is 20 mg per day
C	1 card with one (1) row of nine (9) NRP104 70 mg capsules, and two (2) rows of nine (9) placebo capsules each row 1 card with three (3) rows of nine (9) Adderall XR® 10 mg capsules each row 1 card with three (3) rows of nine (9) placebo capsules each row	Subjects whose optimal Adderall XR® dose is 30 mg per day

Efficacy Assessments
The protocol-defined primary efficacy variable was the SKAMP-DS, an indication of deportment which consisted of items 5-8 from the SKAMP rating scale (Swanson, Kotkin, Agler, M. Flynn and Pelham rating scale; Wigal et al, 1998), a 13-item independent observer rating of subject impairment (7-point scale) of classroom-observed behaviors. It was collected during each of 8 classroom sessions, occurring at 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours post morning dose on Day 7 of each double-blind week. No key secondary variables were identified.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:

- were randomized
- had at least one SKAMP-DS treatment average score post randomization available (defined as having at least six valid measurement values of individual sessions)

Of note, the sponsor did not modify ITT population definition to include all randomized subjects with at least one SKAMP-DS score post randomization as they had agreed in their 1/24/04 and 2/3/05 submissions. According to a 7/21/06 email from Yeh-Fong Chen, Ph.D., statistical reviewer, there was no difference in efficacy results with this modification of the ITT population definition.

The primary outcome measure was the average of SKAMP-DS scores across the treatment assessment day. This measure was analyzed using a mixed-effects model of analysis of variance (ANOVA) for the ITT population. The ANOVA model defined treatment (3 levels) and period (3 levels) as fixed effects, and subject-within-site as random effect. The 3 treatment levels are 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 set at the significance level of 0.05.

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

Missing data for individual items were assessed for each assessment of each scale and imputed with the mean score of the corresponding assessment and rounded up to the nearest integer if the number of items with missing data or invalid was less than or equal to 20% of total item number. Otherwise, the assessment score was set to missing.

The calculation of the SKAMP average across the 8 sessions of a treatment assessment day required at least six valid measurement values of individual sessions; otherwise, the SKAMP average was set to missing for that treatment.

Incomplete data resulting from either early study termination or unavailability was set as missing in the statistical analyses.

Baseline Demographics
The table below displays the demographic characteristics of the randomized patient sample by optimal dose cohort. Since this was a crossover study and the majority of patients received all treatments, no comparisons among treatments were made. No patient under age 6 or over age 12 participated in this study. There were no major differences between the 3 optimal dose cohorts with respect to age or gender. With respect to race, there were no Hispanic patients in Cohort A, compared to about 20% in Cohorts B and C. However, because of the study's crossover design, this is unlikely to have had a significant impact on the study results.

TABLE 10.1.2 : STUDY 201[37]
BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION[38]

Optimal Dose Cohort[39] (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
A (10)	7.8	6-10	70	30	70	20	0	10
B (17)	9.6	7-12	65	35	59	18	24	0
C (25)	9.2	6-12	60	40	48	28	16	8

[37] Figures may not add up to 100% due to rounding.
[38] This information was not provided for the ITT population, and was requested in a 7/17/06 email.
[39] A=NRP104 30 mg, Adderall XR 10 mg or placebo; B=NRP104 50 mg, Adderall XR 20 mg or placebo; C=NRP104 70 mg, Adderall XR 30 mg or placebo

Baseline Severity of Illness
The sponsor did not provide baseline SKAMP-DS scores by optimal dose cohort.

The table below displays the baseline CGI Severity of Illness item score by optimal dose cohort. There were no major differences between the 3 optimal dose cohorts.

TABLE 10.1.3 : STUDY 201[40]
BASELINE DEMOGRAPHICS, RANDOMIZED POPULATION[41]

Optimal Dose Cohort[42] (n)	CGI Severity 4-Moderately (%)	CGI Severity 5-Markedly (%)	CGI Severity 6-Severely (%)
A (10)	60	30	10
B (17)	65	18	18
C (25)	60	20	20

Patient Disposition
A total of 52 patients were included in the database. Two patients, both from optimal dose cohort A, terminated the study within the first double-blind treatment week after randomization while they were on placebo treatment. Major reasons for their discontinuations were adverse event (viral gastroenteritis) and lost-to-follow-up. They did not have any efficacy measures done post randomization, and were not included in the ITT population. The ITT population included 50 patients (8 optimal dose Cohort A patients, 17 optimal dose Cohort B patients, and 25 optimal dose Cohort C patients).

All of the subjects in the ITT population completed the study.

Dosing Information
This was a fixed dose study.

Concomitant Medications
The concomitant use of medications listed below were not allowed during the trial: Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors including STRATTERA™, antipsychotics, neuroleptics, anxiolytics, benzodiazepines or benzodiazepine derivatives, psychostimulants, methylphenidate, amphetamines (including sympathomimetics, appetite suppressants, modafinil, and pemoline), cough/cold preparations containing stimulants, other medications containing amphetamine or

[40] Figures may not add up to 100% due to rounding.
[41] This information was not provided for the ITT population.
[42] A=NRP104 30 mg, Adderall XR 10 mg or placebo; B=NRP104 50 mg, Adderall XR 20 mg or placebo; C=NRP104 70 mg, Adderall XR 30 mg or placebo

pemoline, clonidine and guanfacine, monoamine oxidase inhibitors (MAOIs), anticonvulsant medications, sedatives, sedative-hypnotics such as zopiclone, sedating antihistamines (as a single preparation or in combination), all investigational medications, and all herbal preparations. Antihypertensives (not to include diuretics) were prohibited. Subjects' current stimulant therapy for ADHD was washed out for at least 3 days prior to the enrollment visit.

With respect to the percentages of safety population patients starting use[43] of various concomitant medications during the open-label Adderall XR titration period of the study, the sponsor provided data broken down by cohort. With respect to the percentages of safety population patients starting use[44] of various concomitant medications during the double blind portion of the study, there were no differences between treatment groups (12% in placebo patients, 12% in NRP 104 patients), and the most frequently used were lidocaine and prilocaine. Of note, the sponsor did not provide the percentages of ITT population dose groups using various concomitant medications during the study.[45]

Information regarding patients identified as protocol violators because of prohibited medication use was not provided. [46]

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.2 in Section 10.3.

For the SKAMP deportment averages, the differences were statistically significant in favor of NRP 104. There was no OC or LOCF analysis performed, since the entire ITT population completed the study.

There was a significant (p=0.005) treatment-by-center interaction in this trial according to a January 23, 2006 email from the statistical reviewer, Yeh-Fong Chen, Ph.D. Dr. Chen clarified in a 7/21/06 email that this interaction was likely due to different amounts of difference between drugs and placebo in the centers. She stated it was a quantitative and not a qualitative interaction, which the Agency generally does not find concerning.

Conclusions
The results of Study 201 provide adequate evidence of the efficacy of NRP104 in the treatment of ADHD versus placebo over 1 week of treatment.

[43] Information for actual use of concomitant medications was not provided.
[44] Information for actual use of concomitant medications was not provided.
[45] This information was requested in a 7/17/06 email to the sponsor
[46] This information was requested in a 7/17/06 email to the sponsor

Study 301[47]

Investigators/Sites
Thirty-nine investigators conducted this study at 64 sites in the U.S. Investigators and sites are listed in Appendix 10.3.3 extracted from the sponsor's submission.

Objectives
By protocol, the objective of this trial was to assess the efficacy and safety of NRP104 compared to placebo in the treatment of children aged 6-12 years with ADHD.

Patient Sample
Important inclusion criteria were:
- age 6 to 12 years, inclusive
- meets DSM-IV-TR criteria for a primary diagnosis of ADHD combined type or predominantly hyperactive-impulsive subtype based on a detailed psychiatric evaluation which reviews the DSM-IV-TR criteria
- baseline ADHD-RS total score greater than or equal to 28
- functioning at age-appropriate intellectual level, as deemed by the Principal Investigator
- BP measurements within the 95th percentile for their gender, height and age
- ECG results within normal range as judged by Physician Investigator

The following were relevant exclusion criteria:
- comorbid psychiatric diagnosis by K-SADS-PL or other symptomatic manifestations that, in the opinion of the examining physician, contraindicates Adderall XR or NRP 104 treatment or confounds efficacy or safety assessments
- history of seizures (exclusive of febrile seizure), tic disorder, or a family history of Tourette's disorder
- weight less than 55 lbs (25 kg)
- significantly overweight or obese in the opinion of the Physician Investigator
- QTc interval greater than 440 msec at the screening visit
- Any specific cardiac condition or family history, which would require exclusion in the opinion of the Physician Investigator
- Use of medications that affect BP or HR (with the exception of the subject's current ADHD therapy) or that have CNS effects or that can affect performance
- Positive urine drug result at screening (with the exception of subject's current ADHD therapy)
- hypertension
- use of clonidine or anticonvulsant drug
- abnormal thyroid function
- clinically significant laboratory abnormalities at screening

[47] Note that important protocol changes are incorporated into my description of the protocol.

- concurrent illness, disability, or other condition that might confound the results of safety or efficacy assessments or that might increase risk to the subject or that, in the investigator's opinion, would prohibit the subject from completing the study or would not be in the best interest of the subject. This would include psychosocial factors that could lead to difficulty complying with the protocol.
- pregnancy or lactation

Design
This was a multicenter, randomized, double-blind, placebo-controlled, parallel group fixed dose study. After a 1-week washout of previous stimulant treatment, eligible patients were randomized to NRP104 (30 mg, 50 mg, or 70 mg treatment groups) or placebo for 4 weeks of treatment. At the conclusion of the study, patients who received at least one dose of the randomized double-blind treatment and did not experience any clinically significant adverse events were eligible to participate in a separate open-label long-term study of NRP104.

Study drug was administered as identical-appearing capsules once daily in the morning. NRP 104 was supplied as 30 mg, 50 mg, and 70 mg capsules. The dosing schedule for the active drug groups is depicted in Table 10.1.3 below.

TABLE 10.1.3: DOSING SCHEDULE

Study Weeks	Treatment Group		
	NRP104 30 mg	NRP104 50 mg	NRP104 70 mg
1	30 mg	30 mg	30 mg
2	30 mg	50 mg	50 mg
3	30 mg	50 mg	70 mg
4	30 mg	50 mg	70 mg

Efficacy Assessments
The protocol-defined primary efficacy variable was the ADHD-RS, which was assessed at baseline and at each study visit (7 ± 2 days apart from the baseline visit and from each other). No key secondary variables were identified.

Efficacy Analysis
The intent-to-treat (ITT) patients were those who:
- were randomized to receive the blind treatment
- had both baseline and at least one post-randomization ADHD-RS total score available based on the CRF data collected

Of note, the protocol does not include having a baseline ADHD-RS total score available in its definition of the ITT population.

The primary outcome measure was change from baseline of the ADHD-RS total score at the last post-randomization treatment week (i.e. Weeks 1 through 4) for which a valid ADHD-RS score was obtained. This measure was analyzed using a two-way analysis of covariance (ANCOVA) model.

The ANCOVA model included treatment (the effect of interest), site, and the corresponding baseline score (the covariate). The site effect was used as a blocking factor in the model to control the potential treatment differences among sites. The null hypothesis stated that there were no differences among the four (4) groups of subjects receiving different doses, including placebo. For the ANCOVA, the type I error rate for rejecting a null hypothesis was set at an alpha level of 0.05.

Based on the results from the ANCOVA model, Dunnett's test for multiple mean comparisons with least-square adjustment, which controls the overall family-wise error rate at the predefined level, was employed to compare the ADHD-RS change from baseline of three (3) active treatment groups to placebo. For the Dunnett's test, the family-wise type I error rate for rejecting a null hypothesis was set at the significance level of 0.05 (2-sided). Due to the possible small number of subjects randomized in some study sites, sites with less than 8 patients in the ITT population were grouped together to construct composite (or pooled) site to be included in the efficacy evaluation where the site variable was used. The composite (or pooled) site was constructed based on the following rules. First, the frequency of subjects in the ITT population was calculated for each study site. Secondly, those sites with less than 8 subjects in the ITT population was selected and sorted by the original site number. Then, these sites were pooled together in that order until the number of subjects was at least 8 in the new composite (or pooled) site. This step was repeated for the remaining sites with less than 8 subjects in the ITT population to form additional composite (or pooled) sites.

SAS PROC GLM was used to conduct this analysis and Type III Sum of Squares estimates were reported. To check if the assumptions of the ANCOVA model were met, residuals were examined through histograms, normal plots, Shapiro-Wilk's test, and plots of residuals versus fitted values. The normality was concluded if one of the following criteria was satisfied: a) the p value of the test statistics (W) was greater than 0.05; and, b) the test statistics (W) was greater than or equal to 0.9. Otherwise, the normality was considered substantially violated.

Should the assumptions for the ANCOVA be found to be substantially violated, a nonparametric ANCOVA would be performed in support of the primary model at treatment endpoint (Koch 1998).

Baseline Demographics
Table 10.1.4 displays the demographic characteristics of the ITT patient sample by treatment group. No patient under age 6 or over age 12 participated in this study. There were no major differences between the 4 treatment groups with respect to age, gender, or race.

TABLE 10.1.4 : STUDY 301[48]
BASELINE DEMOGRAPHICS, ITT POPULATION

TX (n)	Age (yrs)		Sex (%)		Race (%)			
	Mean	Range	Male	Female	White	Black	Hispanic	Other
NRP104 70 mg (73)	8.7	6-12	71	29	56	23	16	4
NRP104 50 mg (71)	8.9	6-12	62	38	46	25	24	4
NRP104 30 mg (69)	9.0	6-12	74	26	51	26	14	9
Placebo (72)	9.4	6-12	69	31	60	22	12	6

Baseline Severity of Illness
Treatment groups had no major differences with respect to mean baseline ADHD-RS total score (42.4 in placebo patients, 43.2 in NRP104 30 mg patients, 43.3 in NRP104 50 mg patients, and 45.1 in NRP104 70 mg patients).

Patient Disposition
A total of 297 patients were enrolled (defined as the number of patients who were either washed out for ADHD therapy or randomized without washout). Seven of these patients terminated prior to receiving randomized treatment. Of these 7 patients, 5 were lost to follow-up, 1 withdrew consent, and 1 did not meet inclusion and exclusion criteria. Five subjects received randomized treatment but did not have any ADHD-RS assessments done post randomization and were excluded from the ITT population. The ITT population included 285 patients (72 placebo patients, 69 NRP104 30 mg patients, 71 NRP104 50 mg patients, and 73 NRP104 70 mg patients).

Dosing Information
This was a fixed dose study.

[48] Figures may not add up to 100% due to rounding.

Concomitant Medications

Psychoactive medications other than the investigational products were not allowed in the trial. The table below, extracted from the sponsor's submission, details the washout periods for stimulant medications and for sedating antihistamines and states prohibited therapies.

Washout Schedule and Prohibited Therapies	
Investigational compounds	Use of any investigational compound (except for NRP104) within 30 days prior to Screening will exclude the subject from this study.
Sedatives, Anxiolytics, Antipsychotics	Use of any antipsychotic, anxiolytic, or sedative-hypnotic medication within 30 days prior to Screening will exclude the subject from this study.
Psychostimulants, Amphetamines and Amphetamine-like agents	Sympathomimetics, appetite suppressants, modafinil, methylphenidate, amphetamine and pemoline should be stopped at least 7 days prior to the Baseline visit. Use of caffeine and tobacco will not exclude the subject. Cough/cold preparations containing stimulants/sympathomimetic agents are not permitted during the dose titration and double-blind periods.
Antidepressants	Use of any antidepressant medication within 30 days prior to Screening will exclude the subject from this study.
Clonidine	Use of clonidine within 30 days prior to Screening will exclude the subject from this study.
Norepinephrine Reuptake Inhibitors	Norepinephrine reuptake inhibitors, such as atomoxetine (Strattera™), are not allowed. Use of atomoxetine within 30 days prior to Screening will exclude the subject from this study.
Antihypertensives	All antihypertensive agents, with the exception of diuretics, are not permitted.
Antihistamines (centrally- and peripherally-active)	The use of sedating antihistamines (as a single preparation or in combination) is not permitted. Sedating antihistamines should be stopped at the Screening visit. Non-sedating antihistamines such as fexofenadine (Allegra®), loratadine (Claritin®), and cetirizine HCl (Zyrtec™) are permitted.

With respect to the percentages of randomized patients taking various concomitant medications prior to randomization[49], there were no major differences between treatment groups (56% in placebo patients, 65% in NRP104 30 mg patients, 53% in NRP104 50 mg patients, and 53% in NRP104 70 mg patients). Other than atomoxetine hydrochloride, methylphenidate hydrochloride, and "psychostimulants and nootropics", the most frequently used were multivitamins and lidocaine. With respect to percentages of randomized patients[50] starting concomitant medications during the double-blind period, there were no major differences between treatment groups (19% in placebo patients, 23% in NRP104 30 mg patients, 28% in NRP104 50 mg patients, and 22% in NRP104 70 mg patients), and the most frequently used were ibuprofen and paracetamol (acetaminophen). Of note, the sponsor did not provide any

[49] This information was not provided for patients using various concomitant medications during the study.
[50] This information was not provided for the ITT population.

information regarding the percentages of ITT population treatment groups using various concomitant medications during the study. [51]

Information regarding patients identified as protocol violators because of prohibited medication use was not provided. [52]

Efficacy Results
Efficacy data displays may be found in the Appendices 10.3.4 to 10.3.5.

For the ADHD-RS total score change from baseline analysis, the differences were statistically significant in favor of NRP104 at endpoint (the last post-randomization treatment week for which a valid ADHD-RS score was obtained) for all three doses when using placebo-adjusted difference. At Weeks 1,2, 3, and 4, the differences were also statistically in favor of NRP104 for all 3 doses.

There was no evidence of a treatment-by-center interaction in this trial according to a January 23, 2006 email from the statistical reviewer, Yeh-Fong Chen, Ph.D.

Conclusions
The results of Study 301 provide adequate evidence of the efficacy of NRP104 in doses of 30 mg/day, 50 mg/day, and 75 mg/day versus placebo over 4 weeks of treatment.

10.2 Line-by-Line Labeling Review

See section 9.4 for a discussion of the clinical changes to labeling based on this NDA.

[51] This information was requested in a 7/17/06 email to the sponsor
[52] This information was requested in a 7/17/06 email to the sponsor

10.3 Appendix to Individual Study Reports

APPENDIX 10.3.1: LIST OF INVESTIGATORS for STUDY 201

Site No.	Address of Trial Facility	Name of Investigator(s)
01	Massachusetts General Hospital 185 Alewife Brook Parkway Suite 2000 Cambridge, MA 02138	Joseph Biederman, M.D. (Principal Investigator) Professor of Psychiatry Harvard Medical School
02	Clinical Study Centers, LLC 9601 Lile Drive, Suite 900 Little Rock, AR 72205	Samuel W. Boellner, M.D. (Principal Investigator) CEO and Chief Medical Director
03	Academy of Healing Arts 901 Rancho Lane, Suite 190 Las Vegas, NV 89106	Ann Childress, M.D. (Principal Investigator) Center for Psychiatry and Behavioral Medicine Inc.
04	Children's Developmental Center 600 South Orlando Ave., Suite 102 Maitland, FL 32751	Frank Lopez, M.D. (Principal Investigator) Private practice

APPENDIX 10.3.2: RESULTS OF PRIMARY VARIABLE SKAMP DEPORTMENT : AVERAGE ACROSS 8 CLASS SESSIONS OF THE TREATMENT ASSESSMENT DAY, ITT POPULATION

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			

APPENDIX 10.3.3: LIST OF INVESTIGATORS STUDY 301

Site No.	Address of Trial Facility	Name of Investigator(s)
01	Massachusetts General Hospital 185 Alewife Brook Parkway Suite 2000 Cambridge, MA 02138	Joseph Biederman, M.D. (Principal Investigator) Professor of Psychiatry Harvard Medical School
02	Clinical Study Centers, LLC 9601 Lile Drive, Suite 900 Little Rock, AR 72205	Samuel W. Boellner, M.D. (Principal Investigator) CEO and Chief Medical Director
03	Academy of Healing Arts 901 Rancho Lane, Suite 190 Las Vegas, NV 89106	Ann Childress, M.D. (Principal Investigator) Center for Psychiatry and Behavioral Medicine Inc.
04	Children's Developmental Center 600 South Orlando Ave., Suite 102 Maitland, FL 32751	Frank Lopez, M.D. (Principal Investigator) Private practice
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Deliberative Process

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APPENDIX 10.3.4: RESULTS OF PRIMARY VARIABLE: ADHD-RS CHANGE FROM BASELINE AT ENDPOINT, ITT POPULATION

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
Baseline: Total score	N	72	69	71	73
	Mean (SD)	42.4 (7.13)	43.2 (6.68)	43.3 (6.74)	45.1 (6.82)
Endpoint: Change from baseline	N	72	69	71	73
	LS Mean (SE)*	-6.2 (1.56)	-21.8 (1.60)	-23.4 (1.56)	-26.7 (1.54)
Comparison: Placebo-adjusted difference	LS Mean (95% CI)† p-value†	0	-15.58 (-20.78, -10.38) <0.0001	-17.21 (-22.33, -12.08) <0.0001	-20.49 (-25.63, -15.36) <0.0001

*Treatment effect: p< 0.0001 (2-way ANCOVA)

† Dunnett's test was used for the construction of CIs and p values

APPENDIX 10.3.5: RESULTS OF PRIMARY VARIABLE: ADHD-RS CHANGE FROM BASELINE BY TREATMENT WEEK, ITT POPULATION

Table 6 ADHD-RS Change from Baseline by Treatment Week for the ITT Population (N=285)

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
Baseline: Total score	N	72	69	71	73
	Mean (SD)	42.4 (7.13)	43.2 (6.68)	43.3 (6.74)	45.1 (6.82)
ADHD-RS Change from baseline:					
Week 1	N	72	69	69	72
	LS Mean (SE)*	-4.4 (1.40)	-16.7 (1.43)	-16.5 (1.42)	-16.5 (1.40)
	LS Mean vs. placebo (95% CI)† p-value†	0	-12.24 (-16.90, -7.58) <0.0001	-12.10 (-16.74, -7.47) <0.0001	-12.10 (-16.72, -7.47) <0.0001
Week 2	N	69	63	66	69
	LS Mean (SE)*	-5.7 (1.38)	-19.3 (1.47)	-21.7 (1.41)	-22.7 (1.39)
	LS Mean vs. placebo (95% CI)† p-value†	0	-13.60 (-18.27, -8.93) <0.0001	-16.02 (-20.60, -11.44) <0.0001	-16.94 (-21.54, -12.34) <0.0001
Week 3	N	60	59	63	66
	LS Mean (SE)*	-9.0 (1.52)	-22.8 (1.54)	-24.8 (1.47)	-27.4 (1.46)
	LS Mean vs. placebo (95% CI)† p-value†	0	-13.79 (-18.81, -8.77) <0.0001	-15.75 (-20.67, -10.82) <0.0001	-18.38 (-23.32, -13.43) <0.0001
Week 4	N	54	57	60	60
	LS Mean (SE)*	-8.8 (1.70)	-22.5 (1.65)	-26.1 (1.58)	-28.0 (1.61)
	LS Mean vs. placebo (95% CI)† p-value†	0	-13.70 (-19.15, -8.26) <0.0001	-17.36 (-22.73, -11.98) <0.0001	-19.23 (-24.69, -13.77) <0.0001

* Treatment effect: p<0.0001 (2-way ANCOVA)

† Dunnett's test was used for the construction of CIs and p values

10.4 Appendix to Integrated Review of Efficacy (Section 6)

APPENDIX 10.4.1.1: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION 6-9 YEARS OLD, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=28)	28	28	28
Mean (SD)	0.9 (0.8)	0.9 (0.8)	1.8 (1.2)
LS Mean (SE)	0.9 (0.2)	0.9 (0.2)	1.8 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-1.0 (-1.2, -0.7)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-1.0 (-1.2, -0.7)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		0.0 (-0.3, 0.3)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 5 of this response			

APPENDIX 10.4.1.2: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION 10-12 YEARS OLD, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=22)	22	22	22
Mean (SD)	0.6 (0.5)	0.7 (0.7)	1.5 (1.0)
LS Mean (SE)	0.6 (0.2)	0.7 (0.2)	1.5 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-0.8 (-1.1, -0.5)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-0.7 (-1.0, -0.4)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		-0.1 (-0.4, 0.2)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 6 of this response			

APPENDIX 10.4.1.3: PRIMARY EFFICACY VARIABLE (ADHS-RS CHANGE FROM BASELINE AT ENDPOINT) BY AGE GROUP [6-9 YEAR OLDS (N=172) AND 10-12 YEAR OLDS (N=113)]; ITT POPULATION, STUDY 301

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
6-9 years-old subjects:					
Baseline score	N	35	43	46	48
	Mean (SD)	42.1 (7.48)	43.6 (6.34)	44.5 (5.97)	45.5 (6.90)
Endpoint: Change from baseline	N	35	43	46	48
	LS Mean (SE)*	-6.8 (2.40)	-22.4 (2.11)	-23.5 (2.06)	-29.0 (2.01)
Comparison: Placebo-adjusted difference	LS Mean	0	-15.56	-16.68	-22.15
	(95% CI)†		(-22.99, -8.13)	(-24.03, -9.34)	(-29.60, -14.71)
	p-value†		<0.0001	<0.0001	<0.0001
10-12 years old subjects:					
Baseline score	N	37	26	25	25
	Mean (SD)	42.7 (6.87)	42.5 (7.29)	40.9 (7.52)	44.2 (6.74)
Endpoint: Change from baseline	N	37	26	25	25
	LS Mean (SE)*	-4.5 (2.18)	-21.4 (2.75)	-24.8 (2.82)	-26.0 (2.74)
Comparison: Placebo-adjusted difference	LS Mean	0	-16.83	-20.29	-21.45
	(95% CI)†		(-25.18, -8.48)	(-28.91, -11.67)	(-29.90, -13.00)
	p-value†		<0.0001	<0.0001	<0.0001

* Treatment effect: p<0.0001 (2-way ANCOVA)

† Dunnett's test was used for the construction of CIs and p values

APPENDIX 10.4.2.1: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION BOYS, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=31)	31	31	31
Mean (SD)	0.9 (0.8)	0.9 (0.8)	2.1 (1.1)
LS Mean (SE)	0.9 (0.2)	0.9 (0.2)	2.1 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-1.1 (-1.4, -0.9)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-1.1 (-1.4, -0.9)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		0.0 (-0.3, 0.3)	

* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects)
Source: Appendix Table 3 of this response

APPENDIX 10.4.2.2: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION GIRLS, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=19)	19	19	19
Mean (SD)	0.5 (0.6)	0.6 (0.7)	1.1 (0.9)
LS Mean (SE)	0.5 (0.2)	0.6 (0.2)	1.1 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-0.6 (-0.8, -0.3)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-0.4 (-0.7, -0.2)**
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		-0.2 (-0.4, 0.1)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 4 of this response			

APPENDIX 10.4.2.3: PRIMARY EFFICACY VARIABLE (ADHS-RS CHANGE FROM BASELINE AT ENDPOINT) BY GENDER [BOYS (N=197) AND GIRLS (N=88)]; ITT POPULATION, STUDY 301

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
Boys:					
Baseline score	N	50	51	44	52
	Mean (SD)	43.6 (7.27)	43.8 (6.64)	43.3 (6.50)	45.2 (6.78)
Endpoint: Change from baseline	N	50	51	44	52
	LS Mean (SE)*	-5.9 (1.88)	-23.8 (1.88)	-24.8 (2.01)	-27.6 (1.81)
Comparison: Placebo-adjusted difference	LS Mean (95% CI)†	0	-17.90 (-24.06, -11.75)	-18.89 (-25.20, -12.58)	-21.67 (-27.77, -15.57)
	p-value†		<0.0001	<0.0001	<0.0001
Girls:					
Baseline score	N	22	18	27	21
	Mean (SD)	39.7 (6.11)	41.3 (6.64)	43.2 (7.23)	44.8 (7.10)
Endpoint: Change from baseline	N	22	18	27	21
	LS Mean (SE)*	-8.1 (3.14)	-19.0 (3.33)	-18.8 (2.88)	-24.8 (3.27)
Comparison: Placebo-adjusted difference	LS Mean (95% CI)†	0	-10.85 (-21.85, 0.14)	-10.68 (-20.73, -0.64)	-16.67 (-28.50, -4.84)
	p-value†		0.0537	0.0345	0.0035

* Treatment effect: p<0.05 (2-way ANCOVA)

† Dunnett's test was used for the construction of CIs and p values

APPENDIX 10.4.3.1: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION CAUCASIANS, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=27)	27	27	27
Mean (SD)	0.8 (0.8)	0.9 (0.9)	1.7 (1.3)
LS Mean (SE)	0.9 (0.2)	0.9 (0.2)	1.7 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-0.8 (-1.1, -0.5)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-0.7 (-1.0, -0.5)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		-0.1 (-0.4, 0.2)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 7 of this response			

APPENDIX 10.4.3.2: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION NON-CAUCASIANS, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=23)	23	23	23
Mean (SD)	0.7 (0.6)	0.7 (0.6)	1.7 (1.0)
LS Mean (SE)	0.7 (0.2)	0.7 (0.2)	1.7 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-1.0 (-1.3, -0.8)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-1.0 (-1.3, -0.8)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		0.0 (-0.3, 0.3)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 8 of this response			

APPENDIX 10.4.3.3: PRIMARY EFFICACY VARIABLE (ADHS-RS CHANGE FROM BASELINE AT ENDPOINT) BY ETHNIC ORIGIN [CAUCASIANS (N=152) AND NON-CAUCASIANS (N=133)]; ITT POPULATION, STUDY 301

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
Caucasian subjects:					
Baseline score	N	43	35	33	41
	Mean (SD)	43.0 (7.07)	42.7 (6.82)	43.2 (7.04)	45.2 (6.79)
Endpoint: Change from baseline	N	43	35	33	41
	LS Mean (SE)*	-4.0 (1.98)	-23.8 (2.32)	-26.1 (2.27)	-26.9 (2.01)
Comparison: Placebo-adjusted difference	LS Mean (95% CI)† p-value†	0	-19.79 (-27.03, -12.55) <0.0001	-22.08 (-29.15, -15.12) <0.0001	-22.88 (-29.52, -16.24) <0.0001
Non-Caucasian subjects:					
Baseline score	N	29	34	38	32
	Mean (SD)	41.6 (7.27)	43.7 (6.59)	43.3 (6.56)	44.9 (6.98)
Endpoint: Change from baseline	N	29	34	38	32
	LS Mean (SE)*	-10.1 (2.81)	-18.5 (2.51)	-20.2 (2.43)	-25.1 (2.67)
Comparison: Placebo-adjusted difference	LS Mean (95% CI)† p-value†	0	-8.41 (-17.48, 0.67) 0.0754	-10.09 (-18.61, -1.58) 0.0158	-15.01 (-23.67, -6.35) 0.0002

* Treatment effect: p<0.01 (2-way ANCOVA)
† Dunnett's test was used for the construction of CIs and p values

APPENDIX 10.4.4.1: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION MILDLY/MODERATELY ILL, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=30)	30	30	30
Mean (SD)	0.9 (0.7)	1.0 (0.7)	2.0 (1.0)
LS Mean (SE)	0.9 (0.2)	1.0 (0.2)	2.0 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-1.1 (-1.3, -0.8)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-0.9 (-1.2, -0.7)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		-0.1 (-0.4, 0.1)	
* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects) Source: Appendix Table 9 of this response			

APPENDIX 10.4.4.2: PRIMARY EFFICACY VARIABLE (SKAMP DEPORTMENT AVERAGE ACROSS 8 CLASS SESSIONS) FOR THE ITT POPULATION MARKEDLY/SEVERLY/EXTREMELY ILL, STUDY 201

Parameter	NRP104	Adderall XR®	Placebo
N (ITT=20)	20	20	20
Mean (SD)	0.6 (0.7)	0.5 (0.7)	1.2 (1.2)
LS Mean (SE)	0.6 (0.2)	0.5 (0.2)	1.2 (0.2)
Difference in LS Mean (95% CI) of NRP104 vs. Placebo			-0.7 (-1.0, -0.4)****
Difference in LS Mean (95% CI) of Adderall XR® vs. Placebo			-0.7 (-1.0, -0.5)****
Difference in LS Mean (95% CI) of NRP104 vs. Adderall XR®		0.0 (-0.2, 0.3)	

* p < 0.05; ** p < 0.01; *** p < 0.001; **** p <0.0001 (2-way ANOVA with treatment and period effects)
Source: Appendix Table 10 of this response

APPENDIX 10.4.4.3: PRIMARY EFFICACY VARIABLE (ADHS-RS CHANGE FROM BASELINE AT ENDPOINT) BY BASELINE SEVERITY OF ILLNESS [MILDLY/MODERATELY ILL (N=102) AND MARKEDLY/SEVERELY/EXTREMELY ILL (N=183)]; ITT POPULATION, STUDY 301

		Placebo	NRP104 30mg	NRP104 50mg	NRP104 70mg
Mildly/Moderately Ill subjects:					
Baseline score	N	27	25	25	25
	Mean (SD)	37.3 (5.52)	39.2 (7.53)	37.6 (5.35)	40.3 (6.55)
Endpoint: Change from baseline	N	27	25	25	26
	LS Mean (SE)*	-8.4 (2.22)	-21.2 (2.09)	-24.5 (2.32)	-25.3 (2.37)
Comparison: Placebo-adjusted difference	LS Mean	0	-12.83	-16.15	-16.90
	(95% CI)†		(-19.89, -5.76)	(-22.71, -9.58)	(-23.79, -10.00)
	p-value†		0.0001	<0.0001	<0.0001
Markedly/Severely/Extremely Ill subjects:					
Baseline score	N	45	44	46	48
	Mean (SD)	45.5 (6.17)	45.4 (4.95)	46.4 (5.25)	47.6 (5.55)
Endpoint: Change from baseline	N	45	44	46	48
	LS Mean (SE)*	-4.2 (2.37)	-22.0 (2.35)	-23.9 (2.28)	-27.1 (2.37)
Comparison: Placebo-adjusted difference	LS Mean	0	-17.81	-19.74	-22.88
	(95% CI)†		(-25.32, -10.29)	(-27.10, -12.39)	(-30.23, -15.53)
	p-value†		<0.0001	<0.0001	<0.0001

* Treatment effect: p<0.0001 (2-way ANCOVA)
† Dunnett's test was used for the construction of CIs and p values

10.5 Appendix to Integrated Review of Safety (Section 7)

APPENDIX 10.5.1: INCIDENCE OF TREATMENT-EMERGENT AE'S ASSOCIATED WITH DISCONTINUATION, RANDOMIZED POPULATION[53] (STUDY 301)

Table 4.4.1 Incidence of Treatment-Emergent AEs Associated with Discontinuation

Preferred Terminology (MedDRA 7.1)	30 mg (n=71) N (%)	AE #	50 mg (n=74) N (%)	AE #	70 mg (n=73) N (%)	AE #	Placebo (n=72) N (%)	AE #	Active Doses (n=218) N (%)	AE #
Any Events	6 (8.5)	7	4 (5.4)	7	10 (13.7)	15	1 (1.4)	1	20 (9.2)	29
Cardiac disorders	0	0	1 (1.4)	1	1 (1.4)	1	0	0	2 (0.9)	2
Ventricular hypertrophy	0	0	1 (1.4)	1	1 (1.4)	1	0	0	2 (0.9)	2
Gastrointestinal disorders	1 (1.4)	1	0	0	3 (4.1)	3	0	0	4 (1.8)	4
Abdominal pain upper	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Dry mouth	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Vomiting	0	0	0	0	2 (2.7)	2	0	0	2 (0.9)	2
General disorders and administration site conditions	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Chest pain	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Infections and infestations	0	0	1 (1.4)	1	0	0	1 (1.4)	1	1 (0.5)	1
Influenza	0	0	0	0	0	0	1 (1.4)	1	0	0
Viral upper respiratory tract infection	0	0	1 (1.4)	1	0	0	0	0	1 (0.5)	1
Investigations	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Weight decreased	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Metabolism and nutrition disorders	1 (1.4)	1	0	0	1 (1.4)	1	0	0	2 (0.9)	2
Decreased appetite	1 (1.4)	1	0	0	1 (1.4)	1	0	0	2 (0.9)	2
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Neck pain	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Nervous system disorders	1 (1.4)	1	1 (1.4)	1	3 (4.1)	3	0	0	5 (2.3)	5
Dizziness	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Lethargy	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Psychomotor hyperactivity	0	0	1 (1.4)	1	1 (1.4)	1	0	0	2 (0.9)	2
Somnolence	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Psychiatric disorders	3 (4.2)	3	2 (2.7)	3	1 (1.4)	2	0	0	6 (2.8)	8

Program: T44_01.sas

Preferred Terminology (MedDRA 7.1)	30 mg (n=71) N (%)	AE #	50 mg (n=74) N (%)	AE #	70 mg (n=73) N (%)	AE #	Placebo (n=72) N (%)	AE #	Active Doses (n=218) N (%)	AE #
Abnormal behaviour	0	0	1 (1.4)	1	0	0	0	0	1 (0.5)	1
Anger	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Flat affect	1 (1.4)	1	0	0	0	0	0	0	1 (0.5)	1
Insomnia	1 (1.4)	1	0	0	1 (1.4)	1	0	0	2 (0.9)	2
Logorrhoea	0	0	1 (1.4)	1	0	0	0	0	1 (0.5)	1
Tic	0	0	1 (1.4)	1	1 (1.4)	1	0	0	2 (0.9)	2
Skin and subcutaneous tissue disorders	0	0	1 (1.4)	1	2 (2.7)	2	0	0	3 (1.4)	3
Pruritus	0	0	1 (1.4)	1	0	0	0	0	1 (0.5)	1
Rash	0	0	0	0	2 (2.7)	2	0	0	2 (0.9)	2
Vascular disorders	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1
Hypertension	0	0	0	0	1 (1.4)	1	0	0	1 (0.5)	1

Program: T44_01.sas

[53] Defined as subjects who were randomized to and received blind investigational product

APPENDIX 10.5.2: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT LABORATORY TEST RESULTS

Laboratory Tests	Outlier Criteria		Source
	Low Limit	Upper Limit	
Hematology			
Hemoglobin	Age 5-7 yrs: <11.5 g/dL Age 8-12 yrs: <11.9 g/dL	All ages: >15.0 g/dL	Agency recommended
Hematocrit	Age 5-7 yrs: <34.5% Age 8-12 yrs: <35.4%	All ages: >50%	Agency recommended
WBC	<4,000/mm^3	>15,000/mm^3	Agency recommended
Neutrophils (absolute)	Level 1: <500/mm^3 Level 2: 500 to <1500/mm^3	None	Agency recommended
Eosinophils (absolute)	None	>500/mm^3	Agency recommended
Platelet Count	<150K/mm^3	>600K/mm^3	Agency recommended
Clinical Chemistry			
Calcium	<2.10 mmol/L	>2.80 mmol/L	Agency recommended
Creatinine	None	Age 4-6 yrs: >97 umol/L Age 7-9 yrs: >106 umol/L Age 10-12 yrs: 114 umol/L	Agency recommended
Glucose	<2.78 mmol/L	>7.77 mmol/L	Agency recommended
Albumin	< 50% LLN	None	Sponsor proposed
Alkaline Phosphatase	None	>= 3 x ULN	Sponsor proposed
ALT	None	>= 3 x ULN	Sponsor proposed
AST	None	>= 3 x ULN	Sponsor proposed
Total Bilirubin	None	>= 34 umol/L	Sponsor proposed
Potassium	<3.0 mmol/L	>5.5 mmol/L	Sponsor proposed
Sodium	<130 mmol/L	>150 mmol/L	Sponsor proposed
Urea Nitrogen	None	>=10.7 mmol/L	Sponsor proposed
Urinalysis			
pH	<4.6	>8.0	Merck Manual, 2006
Specific Gravity	<1.001	<1.035	Merck Manual, 2006
Blood	Negative vs. non-Negative		Merck Manual, 2006
Glucose			
Ketones			
Protein			

Note: ULN = upper limit of the normal range from the laboratory; LLN = low limit of the normal range from the laboratory.

APPENDIX 10.5.3: NUMBER (%) OF PATIENTS WITH OUTLIER VALUES IN STUDY 301

Lab Tests	Short-Term: 104.301 Placebo (n=72)		Short-Term: 104.301 NRP104 (n=218)	
	Baseline	Endpoint	Baseline	Endpoint
Hematology				
WBC:				
>1,5000/mm^3	0	0	1 (1%)	2 (1%)
<4,000/mm^3	3 (4%)	5 (7%)	6 (3%)	6 (3%)
Eosinophils:				
>500/mm3	10 (14%)	8 (11%)	24 (11%)	14 (6%)
Neutrophils /mm3:				
<500/mm3	0	3 (4%)	3 (1%)	0
500/mm3 to <1,500/mm3	4 (6%)	5 (7%)	6 (3%)	10 (5%)
Hemoglobin (g/dL):				
High (All Ages: >15.0 g/dL)	1 (1%)	0	3 (1%)	6 (3%)
Low (Age 5-7 yrs: <11.5 g/dL, Age 8-12 yrs: <11.9g/dL)	1 (1%)	0	8 (4%)	6 (3%)
Hematocrit (%):				
High (All Ages: >50%)	0	0	0	1 (1%)
Low (Age 5-7 yrs: <34.5%, Age 8-12 yrs: <35.4%)	2 (3%)	1 (1%)	7 (3%)	5 (2%)
Platelet count:				
>600 K/mm3	0	0	0	0
<150 K/mm3	0	0	1 (1%)	0
Chemistry				
Albumin (g/dL):				
<50% LLN	0	0	0	0
Alkaline Phosphatase (IU/dL):				
>= 3 x ULN	0	0	0	0
Bilirubin total (umol/L):				
>= 34	0	0	0	0
Calcium (mmol/L):				
>2.80	0	0	0	0
<2.10	0	0	1 (1%)	0
Creatinine (umol/L):				
High	0	0	0	1 (1%)
Glucose (mmol/L):				
>7.77	0	0	2 (1%)	0
<2.78	1 (1%)	1 (1%)	5 (2%)	3 (1%)
Potassium (mmol/L):				
>5.5	7 (10%)	2 (3%)	9 (4%)	12 (6%)
<3.0	0	0	0	0
Sodium (mmol/L):				
>150	0	0	0	0
<130	0	0	1 (1%)	0

Urinalysis				
pH:				
>8.0	0	0	0	0
<4.6	0	0	0	0
Specific Gravity:				
>1.035	2 (3%)	0	0	1 (1%)
<1.001	0	0	0	0
Ketones:				
Non-Negative	0	0	5 (2%)	13 (6%)
Protein:				
Non-Negative	5 (7%)	7 (10%)	27 (12%)	43 (20%)
Blood:				
Non-Negative	1 (1%)	2 (3%)	3 (1%)	4 (2%)
Glucose:				
Non-Negative	0	0	0	0

Source: Appendix 12-I, Tables 1 (hematology), 2 (chemistry), and 3 (urinalysis)

APPENDIX 10.5.4: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN RESULTS

Systolic BP	<5th or >95th percentile (PCT) for age, gender, and height [1]
Diastolic BP	<5th or >95th percentile (PCT) for age, gender, and height [1]
Pulse	<60 bpm or >140 bpm
Temperature	<95 F or >100.4 F

[1] Sponsor note: based on the Blood Pressure Table for Children and Adolescents, May 2004, National Heart, Lung, and Blood Institute.

APPENDIX 10.5.5: NUMBER (%) OF PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT VITAL SIGN RESULTS OBSERVED AT ENDPOINT AND EACH TREATMENT WEEK

Vital Signs	Placebo (n=72)		30 mg (n=71)		50 mg (n=74)		70 mg (n=73)	
Systolic BP (mmHg)	<5th PCT	>95th PCT	<5th PCT	>95th PCT	<5th PCT	>95th PCT	<5th PCT	>95th PCT
Endpoint	0	4 (6%)	0	6 (8%)	2 (3%)	7 (9%)	0	6 (8%)
Week 1	0	6 (8%)	1 (1%)	7 (10%)	1 (1%)	7 (9%)	0	2 (3%)
Week 2	2 (3%)	4 (6%)	0	5 (7%)	0	8 (11%)	1 (1%)	6 (8%)
Week 3	1 (1%)	5 (7%)	0	8 (11%)	0	11 (15%)	1 (1%)	4 (5%)
Week 4	0	2 (3%)	0	5 (7%)	1 (1%)	6 (8%)	0	3 (4%)
Diastolic BP (mmHg)	<5th PCT	>95th PCT	<5th PCT	>95th PCT	<5th PCT	>95th PCT	<5th PCT	>95th PCT
Endpoint	0	5 (7%)	0	6 (8%)	0	4 (5%)	0	4 (5%)
Week 1	0	3 (4%)	0	1 (1%)	0	4 (5%)	0	3 (4%)
Week 2	0	7 (10%)	0	3 (4%)	0	2 (3%)	0	2 (3%)
Week 3	0	3 (4%)	0	5 (7%)	0	6 (8%)	0	4 (5%)
Week 4	0	3 (4%)	0	5 (7%)	0	3 (4%)	0	3 (4%)
Pulse (bpm)	<60 bpm	>140 bpm	<60 bpm	>140 bpm	<60 bpm	>140 bpm	<60 bpm	>140 bpm
Endpoint	1 (1%)	0	2 (3%)	0	1 (1%)	0	0	0
Week 1	0	0	2 (3%)	0	0	0	0	0
Week 2	0	0	1 (1%)	0	0	0	0	0
Week 3	1 (1%)	0	0	0	0	0	0	0
Week 4	0	0	1 (1%)	0	1 (1%)	0	0	0
Body Temp. (F)	<95 F	>100.4 F	<95 F	>100.4 F	<95 F	>100.4 F	<95 F	>100.4 F
Endpoint	0	0	0	0	1 (1%)	0	1 (1%)	0
Week 1	1 (1%)	0	1 (1%)	0	0	1 (1%)	1 (1%)	0
Week 2	0	0	0	2 (3%)	0	1 (1%)	0	0
Week 3	0	0	0	0	0	0	1 (1%)	1 (1%)
Week 4	0	0	0	0	1 (1%)	0	0	0

Note: PCT stands for percentile by gender, age and height. Subjects' height PCT was based on the 2000 CDC Growth Chart.
Source: Appendix 19-I Tables 1 (SBP), 2 (DBP), 3 (pulse), and 4 (temperature)

APPENDIX 10.5.6: CRITERIA FOR DETERMINING POTENTIALLY CLINICALLY IMPORTANT VALUES IN ECG RESULTS

Heart Rate	<60 bpm or >140 bpm
QT or QTc	450 to 479 msec 480 to 499 msec >=500 msec
PR	<0.09 sec or >0.17 sec
QRS	<0.04 sec or >0.09 sec

APPENDIX 10.5.7: NUMBER (%) OF PATIENTS WITH ECG PARAMETER VALUES POST BASELINE OF POTENTIAL CLINICAL INTEREST

ECG Measures	Placebo N=72	NRP104 30mg N=71	NRP104 50mg N=74	NRP104 70mg N=73
QT Interval: >=500 msec	0	0	0	0
480-499 msec	0	0	0	0
450-479 msec	0	0	0	0
QTc-B Interval: >=500 msec	0	0	0	0
480-499 msec	0	0	0	0
450-479 msec	0	3 (4%)	2 (3%)	1 (1%)
QTc-F Interval: 500+ msec	0	0	0	0
450-499 msec	0	0	0	0
450-479 msec	0	0	0	0
Heart Rate: >140 bpm	0	0	0	0
<60 bpm	4 (6%)	2 (3%)	3 (4%)	3 (4%)
PR Interval: >0.17 sec	3 (4%)	2 (3%)	0	5 (7%)
<0.09 sec	0	0	1 (1%)	1 (1%)
QRS Interval: >0.09 sec	9 (13%)	13 (18%)	13 (18%)	16 (22%)
<0.04 sec	0	0	0	0

Source: Appendix 24-I Table 1

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/s/

Michelle Chuen
7/28/2006 04:10:45 PM
MEDICAL OFFICER

Ni Aye Khin
9/1/2006 01:41:27 PM
MEDICAL OFFICER
I agree that this NDA be considered approvable; see memo to file for additional comments.

MEDICAL OFFICER CONSULT

PEDIATRIC AND MATERNAL HEALTH TEAM

SPONSORS: New River Pharmaceuticals

NAME: NRP204 (lisdexamfetamine dimesylate)

NUMBER: NDA 21-977

CLASS: ADHD

MEDICAL OFFICER: Hari Cheryl Sachs, MD, FAAP

REVIEW DATE: June 7, 2006

REVIEW SUMMARY:

NRP204 (lisdexamfetamine dimesylate) is a potentially new chemical entity to treat ADHD. The Pediatric and Maternal Health Team has been consulted to help provide guidance to the sponsor regarding outlier criteria for laboratory tests (chemistry, hematology, and urinalysis), vital signs (blood pressure, pulse and body temperature) and electrocardiograms (HR, QT, QTc, PR interval and QRS interval). In general, the Sponsor should use age- and gender- appropriate norms for hematologic and chemistry parameters that differ from adults and the outlier data should be adjusted to reflect clinically significant changes. Specific suggestions are recommended for alkaline phosphatase, glucose, calcium, creatinine and all the hematologic parameters. All vital signs should be measured at rest and compared to age-appropriated norms. In particular, BP should be measured via appropriate cuff size and interpreted per published BP nomograms. EKG parameters should be interpreted by a pediatric cardiologist familiar with age-appropriate norms. QTc findings should be presented as recommended per the QTc guidance.

SIGNATURES

Reviewer: *Hari Cheryl Sachs, MD, FAAP* **Date:** June 2, 2006

Acting Team Leader: *Jean Temeck, MD* **Date:** June 2, 2006

Acting Division Director: *Lisa Mathis, M.D.* **Date:** June 7, 2006

M E M O R A N D U M

Date received: May 10, 2006
Date assigned: May 10, 2006
Date review completed: June 2, 2006
Due Date requested: June 7, 2006

From: Hari Cheryl Sachs, M.D., Medical Officer
Pediatric and Maternal Health Team
Office of New Drugs – Immediate Office

Through: Jean Temeck, M.D., Acting Team Leader
Lisa Mathis, M.D. OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs – Immediate Office

To: Thomas Laughren, M.D., Division Director
Division of Psychiatry Drug Products

Subject: Outlier criteria

Name of Drug: NRP204 (lisdexamfetamine dimesylate)

Sponsor: New River Pharmaceuticals

NDA Number: 21-977

Formulation: Capsule, Oral

Proposed Indication: Attention deficit hyperactivity disorder (ADHD)

Consult question: The Pediatric and Maternal Health Team has been consulted to help provide guidance to the sponsor regarding outlier criteria for laboratory tests (chemistry, hematology, and urinalysis), vital signs (blood pressure, pulse and body temperature) and electrocardiograms (HR, QT, QTc, PR interval and QRS interval).

Material Reviewed
Sponsor's submission (NDA 21-977 submitted 3/16/06)
Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
(http://www.fda.gov/cder/guidance/6922fnl.htm)
Brief literature review (normal ranges and children)
Selected pediatric texts (see references)

Background Information:

NRP 204 (lisdexamfetamine dimesylate) is a new molecular entity to be used for the treatment of ADHD in children aged 6 to 12 years.

Summary of submission:

The Sponsor (New River Pharmaceuticals) has submitted data on patients ages 6 to 12 years. New River proposes to perform analyses on outliers for laboratory parameters (see Appendix I) and for patients with either vital sign (see Appendix II) or EKG changes from baseline (see Appendix III). Hemoglobin and hematocrit values are gender specific.

Review and Discussion:

A. Normal Laboratory Values

Laboratory reference values vary with the analytic method used, which depends on the institution. The Sponsor's proposed laboratory analyses (abstracted from Table 12-1 Appendix I) are compared to those provided in several representative pediatric references: a pediatric handbook (Harriet Lane), text (Oski's Principles and Practice of Pediatrics), [redacted] and Children's Hospital National Medical Center Laboratories (See Tables I and II).

1. Chemistry

Of note, in children, several parameters differ from those in adults. For example, alkaline phosphatase and serum calcium levels are significantly higher in growing children and adolescents due to rapid growth spurt compared with adults. Creatinine levels in children are lower than adults, and increase with growth and muscle mass. In addition, depending on the laboratory, there may be gender differences in creatinine kinase (CK) levels.

Several parameters (glucose, calcium and creatinine) suggested by the Sponsor appear to differ significantly from accepted norms in children and adults. Hypoglycemia in children is usually < 45-50 mg/dl (2.5 to 2.78 mmol/L). The definition of hyperglycemia varies with food intake. A fasting blood sugar $\geq$ 126 mg/dl ($\geq$7 mmol/L) or a random glucose $\geq$200 mg/dl ($\geq$11.1) is considered diagnostic for diabetes, while a fasting blood sugar of 100-125 mg/dl (6.1-6.9 mmol/L) or a post-prandial glucose of 140-199 mg/dl (7.77-11.0 mmol/L) is considered to be impaired (American Diabetes Association Position Statement 2006, Gahagan 2003). Hypercalcemia is considered to be a calcium level > 1 mg/dl above the normal range (calcitriol labeling), which depends on the laboratory or > 11.2 mg/dl (2.8 mmol/L) per paricalcitol labeling.

2. Urinalysis

Although no specific information regarding urinalysis was submitted to us, urinalysis may be interpreted per adult norms.

3. Hematology

In general the hematologic parameters should be compared to age appropriate norms. After puberty, hemoglobin and hematocrit values are greater in males compared to females. These parameters are also higher in adolescents compared to children. However, hemoglobin and hematocrit are equivalent in prepubertal males and females. (Cheung 2004). A hemoglobin < 11.5 and the equivalent hematocrit < 34.5 is considered

by the CDC to be diagnostic of anemia in children aged 5 to < 8 years. Similarly for children ≥ 8 to12 years, a hemoglobin < 11.9 and a hematocrit < 35.4 meet the CDC definition for anemia (MMWR 1998).

Thrombocytopenia is defined as a platelet count < 150K, whereas thrombocytosis is considered to be a platelet count > 600K (see anagrelide labeling). Clinically important leukocytosis is a total white cell count > 15,000/mm^3 and leukopenia is < 4,000/mm^3 (Merck Manual). Neutrophil counts should be reported as absolute neutrophil count (ANC). Clinically significant neutropenia is defined as ANC < 1500/mm^3 with profound neutopenia as ANC < 500/mm^3. Eosinophilia is defined as an absolute eosinophil count > 500/mm^3 (McMillan 1999).

Table I: Normal Laboratory Values (Chemistry)

Parameter	Proposed	Harriet Lane	Oski	CNMC	[redacted]	Comments
ALT (U/L)						
4- 6 year	≥ 3 x ULN	10-40 (M) 7-35 (F)	6-39	24-49 (M) 24-44 (F)	10-25	Acceptable
7-9 year					10-35	
10-11 year					10-35 (M) 10- 30 (F)	
12 year				24-68 (M) 24-44 (F)	10-55 (M) 10-30 (F)	
> 21 years				30-65	3- 60 (M) 3-40 (F)	
Alkaline Phosphatase (U/L)						
4-6 year	≥ 3 x ULN	100-320	100-320	191-450	90-300 (M) 100-300 (F)	Acceptable provided the ULN is age-appropriate since normal values for growing children exceed adult norms;
7-9 year				218-499 (F)	90-315 (M) 70-325 (F)	
10-11 year		100-390 (M) 100-320 (F)	100-390 (M), 100- 320 (F)	174-624 (M) 169- 657 (F)	40-360 (M) 50- 330 (F)	
12 year				245-584 (M) 141- 499 (F)		
> 21 years		30-120	Not listed > 18 years	50-136	38- 126	
AST (U/L)						
4-6 year	≥ 3 x ULN	15-50	23-58	10-47	15-40 (M) 13-35 (F)	Acceptable
7 year						
8-9 year		15-40	16-46	10-36 (M) 5-36 (F)		
10-11 year		10-60				
12-19 year		15-45	16-38 (> 14 years)	10-36 (M) 5-26 (F)		
> 21 years		0-35		15-37	0- 35	
CK (U/L)						
4-6 years	≥ 2 x ULN	15-105 (M) 10- 80 (F)	Range listed for newborn: 76- 600	31-152 (M) 25-177 (F)	18- 158 (M) 8-147 (F)	Acceptable; may be gender specific
7-9 years					2-177 (M) 26-145 (F)	
10-11 years				31- 152 (M) 31-172 (F)	6-251 (M) 5-137 (F)	
> 12 year						
> 21 years			38-174 (M) 96- 140 (F)	33-145 (M) 21-232 (F)	55-170 (M) 30-135 (F)	
LDH (U/L)						
4-6 year	≥ 3 x ULN	110-295	150-300	155-280	100-295	Acceptable
7-9 year				141- 237		
10-11 year				141-231 (M) 129- 225 (F)		
12-19 year		100-190	0- 250	141-231 (M) 129-205 (F)	100-190	
> 21 years		0- 220		100-190	45- 90	
Total bilirubin (umol/L)						
Child	≥ 34	5-21	< 17	< 0.8 mg/dl (< 13.6) (M) < 1.0 mg/dl (< 17.1) (F)	0.3- 1.2 (5.24- 20.52)	Acceptable
> 21 years				0.6- 1.0 mg/dl (10.2-17.1) (M) 0.0-1.0 mg/dl (0-17.1) (F)	0.3- 1.0 (5.24- 17.1)	
Albumin (g/dL)						
6-8 y	< 50 % LLN	3.3-5.0	3.7- 5.6	3.8- 5.2	3.2- 4.7 (M) 2.9- 4.2 (F)	Acceptable
9-11 y		3.2-5.0				
12- 16 y		3.2-5.1				
> 21 years		3.1- 5.4		3.4- 5.0	3.7-5.1	
Glucose mmol/L						
6-12 years	< 2.5 or > 8.88	3.3- 5.6	3.33-5.83	54- 117 mg/dl (3.0- 6.49)	Fasting: 60-99 mg/dl (3.33- 5.49) Postprandial: < 140 mg/dl (7.77)	Range needs to be adjusted: suggest < 2.78, > 7.77 if random;
> 21 year		3.9- 6.4	3.89- 6.38	70-110 mg/dl (3.89- 6.1)	Fasting (< 5.5) Random (< 7)	

ULN= upper limit of normal LLN- lower limit of normal N/A- Not available

Note: units were converted to SI units per JAMA author instructions

Table I: Normal Laboratory Values (Chemistry), continued

Parameter	Proposed	Harriet Lane	Oski	CNMC	------ ----------	Comments
Sodium mmol/L						
6- 12 years	< 130 or > 150	133-146	135- 148	132-141	135-146	Acceptable
Adult		135-148		140-149	135-145	
Potassium mmol/L						
6-12 years	< 3 or > 5.5	3.4-4.7	3.5-5.0	3.3- 4.7	3.4-4.7	Acceptable
> 21 years		3.5-5.0		3.6- 5.2	3.5- 5.0	
Calcium mmol/L						
4-6 year	< 2.1 or > 2.88	2.2-2.7	2.0-2.6	9.0- 10.1 mg/dl (2.25-2.53)	8-10.6 mg/dl (2-2.65)	Confirm laboratory reference range. Recommend upper limit be lowered to 2.80 (11.20 mg/dl)
7-11 year						
12 year				9.0-10.6 mg/dl (2.25-2.65)	8-10.3 mg/dl (2-2.58)	
> 21 years		2.1- 2.6	2.1- 2.6	8.5- 10.1 (1.7- 2.52)	9- 10.5 mg/dl (2.25-2.62)	
BUN mmol/L						
4-6 year	> 10.7	1.8- 6.4	2- 7.6	6- 17 mg/dl (2.1- 6)	N/A	Acceptable
7- 12 year				7- 21 mg/dl (2.5- 7.5)		
> 21 years		2.5- 7.9		7- 18 mg/dl (2.5- 6.4)	8-20 mg/dl (2.9- 7.1)	
Creatinine umol/L						
4-6 year	> 153	27-62	27- 62	0.2-0.8 mg/dl (18- 71)	0.5- 0.8 mg/dl (44-71)	Normal values for children are lower, upper limit of normal should be lowered: suggest > 97 for 4-6 years; >106 for 7-9years; >114 for 10-12
7-9 year					0.6-0.9 mg/dl (53-80)	
10- 12 year		44-88	44- 88	0.5-1.1 mg/dl (44- 97)	0.6- 1.0 mg/dl (53-88)	
> 21 years		52-115 (M) 53-97 (F)	53-115 (M) 44-106 (F)	0.6- 1.3 mg/dl (53-115)	0.7- 1.2 mg/dl (106)	

ULN= upper limit of normal LLN- lower limit of normal N/A- Not available

Note: units were converted to SI units per JAMA author instructions

Table II: Normal Laboratory Values (Hematology)

Parameter	Proposed	Harriet Lane	Oski	CNMC	[redacted]	Comments
WBC (x 10^3)						
6-7 years	≤ 2.8 or > 16	4.5-13.5	5- 14.5	4.31-11.0 (M) 4.27- 11.4 (F)	4-12	Range appears to be too wide and should be narrowed: suggest <4 and >15
8			4.5- 13.5			
9-11 years					4-10.5	
12-16 years						
> 21 years		4.5-11.0	4.5- 11	3.91- 8.77 (M) 4.37- 9.68 (F)	4.5- 11	
Hemoglobin (g %)						
6-9 years	M ≤ 11.5 F ≤ 9.5	> 11.5	> 11.5	10.7 -13.4 (M) 10.6- 13.2 (F)	11.5-14.5	Levels in prepubertal boys and girls are similar; suggest < 11.5 for children 5-7 and < 11.9 for children 8-12 years. If pubertal, Hgb <12 for F and <13 for M.
10-12 years					12-16	
12-18 years		> 13 (M) > 12 (F)	> 13 (M) > 12 (F)	Not obtained	Not obtained	
> 21 years		> 13.5 (M) > 12 (f)		11.9- 15.4 (M) 10.6- 13.5 (F)	8.7- 11.2 (M) 7.4- 9.9 (F)	
Hematocrit (%)						
6-9 years	M ≤ 37 F ≤ 32	> 35	> 35	32.2-39.8 (M) 32.4-39.5 (F)	33-43	Outlier range for females appears to be too low: suggest < 34.5 for children 5-7 and 35.4 for children 8-12 years. If pubertal, Hct <36% for F and <37% for M.
9-11 years					35-49	
12-18 years		> 41 (M) > 36 (F)	> 37 (M) > 36 (F)			
> 21 years		> 41 (M) > 36 (F)		36.2- 46.3 (F) 32.9- 41.2 (F)	40- 54 (M) 37- 47 (F)	
Platelets (10^3/mm)						
6-12 years	≤ 75 or > 700	150-350	150-300	206- 369 (M) 214-459 (F)	150-400	Range is too wide and should be narrowed; suggest <150 and > 600K
12-18 years						
> 21 years		150-350		151- 304 (M) 186- 353 (F)	150-400	
Neutrophils (10^3/mm)						
6- 7 years	≤ 15 %	1.5-8.0 (51 %)	1.5- 8.0 (51 %)	45-50 %	32-74 %	Data should be presented as ANC < 500 and <1500
8-9 years		1.5- 8.0 (53 %)	1.5- 8.0 (53 %)			
10-15 years		1.5-8.5 (54 %)	1.8- 8.0 (54 %)		42-74 %	
16- 20 years		1.8- 8.0 (57 %)	1.8- 8.0 (57 %)			
> 21 y		1.8- 7.7 (59%)	1.8- 7.7 (57 %)	50-65 %	47- 77 %	
Eosinophils(10^3/mm)						
6- 7 years	≥ 10 %	0.2 (3 %)	0.2 (3 %)	0- 3 %	0- 0.4 (1-7 %)	Suggest absolute eosinophil count > 500
8-9 years		0.2 (2 %)	0.2 (2 %)			
10-15 years		0.2 (2 %)	0.2 (2 %)			
16- 20 years		0.2 (3 %)	0.2 (3 %)			
> 21 years		0.2 (3 %)	0.2 (3 %)	0- 3 %	0.3- 7 %	

B. Normal Vital Signs

Analysis of changes in blood pressure (BP), pulse, temperature and respiratory rate will be performed by the Sponsor. For BP, The Sponsor proposes to report the number and percent of children with systolic blood pressure (SBP) < 120 and diastolic blood pressure (DBP) > 80 at baseline who exceed SBP of > 120 or fall below DBP < 80 after treatment (see Appendix II).

Reviewer comment: The Sponsor's proposal is not acceptable. In children, BP levels vary by age, height and gender (Cromwell 2005). Normal values are available in BP nomograms. These nomograms are available in pediatric reference texts (Rudolph, Oski, and Gellis) or reviews of hypertension in children (Crowell 2005, Fourth Report). The Harriet Lane in particular lists the 50th, 90th 95th and 99th percentile by age, gender and height for both SBP and DBP. Consequently, BP should be analyzed by the number and percent of patients exceeding the 90th, 95th and 99th percentiles for SBP and DBP before and after treatment; and the number of patients with normal values at baseline who exceed these parameters after treatment. The Sponsor should confirm that BP was measured with a correctly sized BP cuff for age. In addition, several measurements (an average of 3) should be performed several minutes apart due to the variability in BP over time.

With regard to heart rate, the Sponsor proposes to analyze the percent of patients whose pulse changed from below 113 bpm [mean + 2 SD (standard deviations)] at baseline to above 113 bpm.

Reviewer comment: There appears to be a typo on page 297 of the protocol, which states the mean + 2 SD is 103. This should be clarified. Heart rate varies with age and is typically higher in children compared to adult norms, decreasing with age. In addition, heart rate varies with activity (e.g., slower at rest) or disease state (e.g., increases with fever. Table III illustrates the normal heart rates for children, according to several pediatric references. Normal references ranges for the 2.5 to 97.5 percentile has been derived recently from a sample of over 1000 children (Wallis 2005) and are included in the table below. Thus, heart rate should be measured at rest and compared with age-appropriate norms. The Sponsor should identify those patients with tachycardia (HR > 140). In addition, the number of patients with significant tachycardia (HR > 180) should also be reported. A summary of accepted normal ranges for heart rate derived from commonly available pediatric resources is presented below:

Table III: Normal Heart Rate in Children (bpm)

Age (years)	**Wallis (2.5-97.5 %tile)**	**Harriet Lane Range (mean)**	**Oski Range**	**Garson**	**Bates**
6	69- 115	60- 130 (100)	60-180	65-133 (100)	65- 125
7	66- 111				
8	63-109			62- 130 (91)	
9	62-108	60- 110 (85)			
10	61- 108		50-180		
11	60- 108				55-115
12	59- 108			60- 119 (85)	

With regard to temperature, the sponsor plans to report the number and percent of patients whose temperature changed from below 99.7 (the mean + 2 SD) to above 99.7.

Reviewer comment: Body temperature should be obtained in a standard manner (e.g., oral) and during a similar time of day, given the diurnal variation in temperature. A clinically significant change would be the number and percent of patients with fever, which is considered to be a core temperature above 100.4°F or 38°C (Goldstein 2005).

The submission we received did not contain a plan for analysis of respiratory rate. This should be provided to the Review Division for comment. Respiratory rates are higher in younger children compared to adults (see Table IV). Wallis, et al. provided 2.5 and 97.5 percentiles for respiratory rate by age and heart rate for 1109 children (Wallis 2005).

Table IV: Respiratory Rates by Age

Age (years)	**Wallis (2.5-97.5 %tile)**	**Harriet Lane (range)**	**Bates**
6	18- 24	20-24	20-40
7	17- 24	18-24	
8	17- 23		
9	16- 23		15-25
10	15- 22	16-22	
11	14- 21		
12	14- 21		

C. Normal EKG parameters

The Sponsor proposes to report the number and percent of patients with QTc measurements $\geq$ 450 to <500 msec and $\geq$ 500 msec, as well as increases in QTc from baseline of > 60 msec and $\geq$ 30 to 59 msec
According to the QTc guidance (http://www.fda.gov/cder/guidance/6922fnl.htm), the following analyses regarding QTc should be performed:

- Absolute prolongation: QTc > 450, QTc > 480 and QTc > 500 msec
- Change from baseline: QTc interval increases > 30 and > 60 msec

Morphologic abnormalities (such as change in U waves) should be incorporated in the analysis. The Guidance also provides formulae for calculating the QTc.
Reviewer comment: the Sponsor should perform an analysis as per the QT guidance.

In addition, as noted above, heart rate varies with age (Wallis 2005). In general, heart rate decreases with age while due to increasing muscle mass, QRS duration slightly increases with age (see Table V below). Of particular clinical significance, the lower limit of HR by ECG (per Garson) is 3-9 years: 60 bpm (ages 3-9 years) and 50 bpm (> 9 years). Supraventricular tachycardia (SVT) is defined as HR > 180 bpm. Finally, QRS axis and amplitude of the P wave vary with age (Garson, Harriet Lane, and University of Chicago).

Table V: EKG Findings in Children by Age

	Harriet Lane	**Garson**	**University of Chicago**
HR (bpm)	Range (mean)	Range to 98th centile (mean)	Range
4-5 years	65- 135 (110)	65- 133 (100)	65-140
6-7 years	60- 130 (100)		
8 year s		62- 130 (91)	60- 130
9- 11 years	60- 110 (85)		
12-15years		60- 119 (85)	65-130
PR interval (sec)	Range (mean)		
4-5 years	0.11- 0.15 (0.13)	0.09- 0.16 (0.12)	0.09- 0.17
6-7 years	0.12- 0.16 (0.14)		
8 years		0.09- 0.17 (0.13)	0.09-0.17
9- 11 years	0.12- 0.17 (0.14)		
12-15years	0.12- 0.17 (0.15)	0.09-0.18 (0.14)	0.09-0.18
QRS duration (sec)	Mean (98th %)		
4-5 years	0.07 (0.08)	0.04- 0.08 (0.06)	0.04- 0.08
6-7	0.07 (0.08)		
8		0.04- 0.09 (0.06)	0.04- 0.09
9- 11 years	0.07 (0.09)		
12-15years	0.07 (0.10)	0.04- 0.09 (0.07)	0.04- 0.09
QTc			
Children > 6 months	$\leq$ 0.44	$\leq$ 0.44	
Adults	$\leq$ 0.44		

Reviewer comment: EKGs should be interpreted by pediatric cardiologists who are familiar with the variations in EKG by age.

Recommendations:

In general, the Sponsor should use age-appropriate norms and their outlier data should be adjusted accordingly (described below). For children that are pubertal (e.g., >Tanner II), laboratory findings should be matched by appropriate gender when applicable, particularly hematologic values (e.g., Hgb and Hct).

Chemistry:

The Sponsor's proposed values for albumin, AST, ALT, LDH, alkaline phosphatase, total bilirubin, BUN, CK, sodium and potassium are acceptable

The following should be adjusted as follows:

Glucose: < 2.78, > 7.77 mmol/L if random;

Calcium: upper limit should be lowered to 2.80 mmol/L

Creatinine: upper limit should be lowered to > 97 umol/L for ages 4 to 6 years, > 106 umol/L for 7 to 9 years and > 114 umol/L for 10 to 12 years.

Hematology:

The Sponsor's proposed values should be adjusted as follows:

Hgb: < 11.5 g% for children ages 5 to <8 years and < 11.9 g% for children ages 8 to 12 years both genders; if pubertal: Hgb < 12 g% for females, < 13 g% for males

Hct: < 34.5 % and < 35.4 % (ages 5 to < 8 and 8 to 12 years, respectively) both genders; if pubertal: Hct < 36 % for females, < 37 % for males

WBC: < 4,000/mm^3 or > 15,000/mm^3

Platelets: < 150K or > 600 K

Neutropenia should be defined by absolute neutrophil counts (ANC) with analysis of ANC < 500/mm^3 and 1500/mm^3

Eosinophilia should be defined as an absolute eosinophil count of 500/mm^3

Vital signs:

All vital signs should be measured at rest and compared to age-appropriated norms. Patients with tachycardia (HR >140) or significant tachycardia (HR > 180) should be identified. BP should be analyzed by the number and percent of patients exceeding the 90th, 95th and 99th percentiles for SBP and DBP before and after treatment; and the number of patients with normal values at baseline who exceed these parameters after treatment. Appropriate cuff size for age should be confirmed. For temperature, a clinically significant change would be the number and percent of patients with fever, which is considered to be a core temperature above 100.4°F or 38°C

EKG:

EKG parameters should be interpreted by a pediatric cardiologist familiar with age-appropriate norms. QTc findings should be presented as recommended per the QTc guidance (absolute QTc > 450, 480 and 500 msec and changes from baseline of > 30 and 60 msec).

APPENDIX 1: Sponsor's Outlier Criteria for Laboratory Values (March 2006)

Table 12-1 Outlier Criteria for Laboratory Values	
Hematology	
Hemoglobin (Male)	≤ 115 g/L
Hemoglobin (Female)	≤ 95 g/L
Hematocrit (Male)	≤ 37%
Hematocrit (Female)	≤ 32%
WBC	≤ 2.8 GI/L or > 16.0 GI/L
Neutrophils	≤ 15%
Eosinophils	≥ 10%
Platelet Count	≤ 75.0 or 700.0 GI/L
Clinical Chemistry	
Alkaline Phosphatase	≥ 3 x ULN
ALT	≥ 3 x ULN
AST	≥ 3 x ULN
LDH	≥ 3 x ULN
Creatine Kinase	≥ 2 x ULN
Total Bilirubin	≥ 34 umol/L
Albumin	< 50% LLN
Glucose	< 2.50 mmol/L or > 8.88 mmol/L
Sodium	<130 mmol/L or > 150 mmol/L
Potassium	< 3.0 mmol/L or > 5.5 mmol/L
Calcium	< 2.10 mmol/L or > 2.88 mmol/L
Urea Nitrogen	≥ 10.7 mmol/L
Creatinine	≥ 153 umol/L

Appendix II: Sponsor's Criteria for Vital sign Abnormalities

Parameter	Baseline	After Baseline
Systolic Blood Pressure	≤ 120 mm Hg	> 120 mm Hg
Diastolic Blood Pressure	≥ 80 mm Hg	< 80 mm Hg
Pulse	≤ 113 or 103 bpm	> 113 bpm

Appendix III: Sponsor's Criteria for ECG intervals

Parameter		
QTc	≥ 500 msec	
	≥ 450 to < 500 msec	
QTc increase from baseline	> 60 msec	
	≥ 30 to 59 msec	

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