CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204370Orig1Orig2s000

<u>OTHER ACTION LETTERS</u>

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204370/Original 1
NDA 204370/Original 2

COMPLETE RESPONSE

Forest Laboratories, Inc.
Attention: Melina Cioffi, PharmD
Associate Director, Regulatory Affairs
Harborside Financial Center
Plaza V, Suite 1900
Jersey City, NJ 07311

Dear Dr. Cioffi:

Please refer to your New Drug Application (NDA) dated November 19, 2012, received November 19, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vyralar (cariprazine) capsules 1.5mg, 3mg, 4.5 mg, 6 mg, (b) (4)

We acknowledge receipt of your amendments dated:

December 13, 2012	April 8, 2013 (2)	July 12, 2013	October 1, 2013
December 18, 2012	May 1, 2013	July 25, 2013	October 2, 2013
January 17, 2013	May 13, 2013	August 13, 2013	October 11, 2013
February 8, 2013	May 15, 2013	August 14, 2013 (2)	October 16, 2013
February 13, 2013	May 22, 2013	August 19, 2013	October 18, 2013
February 14, 2013 (2)	May 24, 2013	August 23, 2013	October 23, 2013
February 20, 2013	May 29, 2013	August 27, 2013	October 25, 2013 (2)
February 25, 2013	May 30, 2013	September 6, 2013	October 28, 2013
February 26, 2013	June 4, 2013	September 9, 2013	November 1, 2013
February 28, 2013	June 11, 2013	September 10, 2013	November 7, 2013
March 6, 2013	June 14, 2013	September 16, 2013 (2)	November 14, 2013
March 19, 2013	June 28, 2013	September 18, 2013	
March 29, 2013 (2)	July 2, 2013	September 19, 2013 (2)	
April 3, 2013	July 8, 2013	September 20, 2013	

NDA 204370 provides for the use of Vyralar (cariprazine) capsules for the following indications which, for administrative purposes, we have designated as follows:

- NDA 204370/Original 1 – Acute treatment of manic or mixed episodes associated with bipolar I disorder
- NDA 204370/Original 2 – Treatment of schizophrenia

The subject of this action letter is NDA 204370/Original 1 and NDA 204370/Original 2.

All future submissions to NDA 204370/Original 1 and NDA 204370/Original 2 should specify the NDA number and the Original number to which each submission pertains.
We have completed our review of NDA 204370/Original 1 and NDA 204370/Original 2, as amended, and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

We believe it has been clearly shown that cariprazine is effective in the treatment of schizophrenia and mania associated with bipolar disorder and that there is evidence of a dose-response between 1.5 mg and 6 mg (b) (4) in schizophrenia. The problem is that there is significant dose-related toxicity, increasing in frequency to the end of the 6-week controlled trials, including several toxicities of major concern, notably akathisia/restlessness, parkinsonism/extrapyramidal symptoms (which could predict rates of tardive dyskinesia), and creatinine phosphokinase elevations (although with relatively few instances in the short-term studies of myoglobinuria or renal damage). (b) (4) It is clear that effectiveness of cariprazine is seen in schizophrenia trials as early as one week at doses of 6 mg to 9 mg and at 2-3 weeks with doses of 3 mg; effectiveness in bipolar mania was seen in study RGH-MD-31 at 7-11 days using a titrated dose of 3 mg to 12 mg. Although we appreciate the lack of complete agreement on the relevant half-lives of cariprazine parent and the didesmethylcariprazine (DDCAR) metabolite, total active drug/metabolite blood levels at 4 weeks are at least 3 times what they were at 5 days (a conservative estimate based on study RGH-188-002 of a 1 mg dose given for 21 days). This indicates that the blood levels of active drug that are effective at week one with a 6 mg dose rise to at least 3-4 times the end-of-week one levels by week 4-6, certainly contributing substantially to toxicity but almost surely not to effectiveness, which, as noted, is observable at one week. We in fact do not yet really know the full extent of accumulation of active moiety at steady state because studies of sufficient duration to assess this have not been carried out. It is important to identify a dosing regimen that will provide a prompt initial response and, (b) (4) maintain effective blood levels without leading to toxic levels.

Dosing of cariprazine is admittedly complicated by its complex metabolism, the equivalent activity of the parent and metabolites, and the different half-lives of the 3 active moieties. It is well-recognized that a long half-life drug can be given as a loading dose (if tolerated) or with early rapid titration, followed by a lower maintenance dose. In the case of cariprazine, although the parent drug half-life is fairly long, constant initial dosing would give near-steady-state levels of parent at about 5 days, the time at which cariprazine is effective. If blood levels at 5-7 days are effective, lower doses will be able to maintain those levels long-term, with an increasing fraction of total active moiety represented by DDCAR. Considering total active drug and metabolites, choosing the initial dose to attain effective blood levels promptly and lowering the subsequent doses to maintain effective levels over time is more complicated than use of a loading dose. The choice of the dosing regimen should be determined initially by modeling and

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subsequently by the controlled clinical trials that we believe are needed to support a resubmission.

The trials we recommend for both schizophrenia and bipolar disorder, which we will be glad to discuss further with you, would (b) (4) The goal would be to maintain levels of active drug/metabolite similar to those attained after 1 week (b) (4) and examine several sustaining maintenance doses, (b) (4) that produced considerably fewer adverse effects.

As indicated, our principal concern is that there appears to be a significant risk of (b) (4) (b) (4) (b) (4) With the available data, it is not possible to identify an appropriate dosing regimen. To resolve this concern and identify a dose that is both effective and safe, you will need to conduct additional controlled studies in schizophrenia and mania in bipolar disorder, using initial fixed loading doses followed by a range of lower fixed doses to maintain the response. (b) (4) We suggest using the available PK data as well as modeling to consider further the loading doses and subsequent dose levels. We believe it will be important to discuss the protocols.

A. Dose-Response Relationships for Efficacy

1. Schizophrenia

It is important to note that 1.5 mg daily, the lowest dose assessed for efficacy in the supportive studies, was effective in the treatment of schizophrenia, although not as effective as higher doses. The schizophrenia studies explored a dose range of 1.5 mg to (b) (4) mg daily. Within the two fixed-dose studies, there were dose-related incremental benefits in efficacy up to 6 mg. In Study RGH-MD-04, the treatment effect was greater for cariprazine 6 mg than 3 mg. The treatment effect for the active comparator (aripiprazole 10 mg) was greater than the effect size for cariprazine 3 mg but was modestly smaller than for cariprazine 6 mg. In Study RGH-MD-16, the treatment effects for the 1.5 mg and 3 mg doses were very similar, and the effect size was larger for 4.5 mg daily, although the 4.5 mg dose was numerically inferior to the active comparator, risperidone 4 mg. Study RGH-MD-05 did not use fixed-doses, but compared dose ranges of 3 – 6 mg and 6 – 9 mg, with average doses of about 5.6 and 8.4 mg. The higher dose range gave a greater response. Study RGH-MD-03 used two dose ranges (1.5 mg to 4.5 mg and 6 mg to 12 mg). Although not considered a supportive study (b) (4) , the study did show a nominally significant effect for the lowest dose range. Significant treatment effects occurred early in the studies, when total active moiety exposures were considerably lower than later exposures, and were far from reaching steady state. The highest doses in each of the pivotal studies resulted in statistically significant effects by Week 1.

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In all but one case, the lower doses resulted in statistically significant effects by Week 2. In Study RGH-MD-04, the effect for the 3 mg dose was significant by Week 3. The effectiveness occurred at blood levels of active moiety well below steady state levels. Together these findings indicate that (b) (4) in the schizophrenia trials.

2. Mania associated with Bipolar Disorder

The mania studies used a dose range of 3 mg to 12 mg daily, with two flexible-dose and one study of two overlapping dose ranges (3 mg to 6 mg and 6 mg to 12 mg daily). As a result, there is less information about dose-response relationships than there is for schizophrenia. The data from RGH-MD-33, however, comparing 3mg to 6 mg and 6mg to12 mg dose ranges, show essentially identical effect sizes at a time when total active moiety is nowhere near a plateau and supporting 6 mg as the maximum dose. These findings are supported by analyses of effect by total blood concentrations in the 3 bipolar studies showing no increase in effect with doses above 3 mg.

B. Safety Findings

The primary dose-related toxicities of concern are akathisia, other extrapyramidal symptoms, and possible muscle injury. Effects on blood pressure and heptatoxicity have also been considered.

1. Akathisia and Extrapyramidal Symptoms

Akathisia and other extrapyramidal symptoms were among the most common and most clinically significant adverse reactions in the cariprazine program. Even at the lowest cariprazine doses (1.5 mg and 3 mg), akathisia was reported for 10.3% of subjects, compared to 4.1% of the placebo group and 8.6% of the risperidone group. Akathisia was reported for 18.1% of subjects in the high-dose cariprazine group (9 mg and 12 mg) and 14.2% of the intermediate dose group (4.5 mg and 6 mg).

Akathisia can be one of the most serious adverse reactions related to antipsychotic treatment. At its most severe, it is an intense subjective sense of inescapable motor tension and restlessness, often accompanied by acute anxiety, agitation, and exacerbation of psychotic or manic symptoms. Akathisia can lead to suicide and other dangerous behavior.

The table below summarizes the rates of akathisia and other extrapyramidal symptoms (EPS) in the controlled schizophrenia and mania studies combined, by dose. The effects are all dose-related.

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Proportion of Subjects with Akathisia, Restlessness, and Extrapyramidal Symptoms in the Controlled Schizophrenia and Mania Trials							
	Placebo	**Cariprazine**				**Risperidone**	**Aripiprazole**
	N = 1026 (%)	1.5 to 3 mg N = 583 (%)	4.5 to 6 mg N = 794 (%)	9 to 12 mg N = 563 (%)	Overall N = 1940 (%)	N = 140 (%)	N = 152 (%)
Akathisia	4.1	10.3	14.2	18.1	14.2	8.6	7.2
Restlessness	2.7	3.8	6.3	6.2	5.5	2.9	3.3
Extrapyramidal Symptoms	9.4	15.6	20.9	25.9	20.8	27.1	5.9

The tables below summarize the akathisia and EPS by individual indication (schizophrenia and mania). The rates of akathisia and EPS were higher in the mania studies, even though the studies were shorter, perhaps related to the higher average doses.

Adverse Event	**EPS and Akathisia in Controlled Schizophrenia Studies**						**Open-label Extension**
	Placebo	Cariprazine			Risperidone 4 mg	Aripiprazole 10 mg	Cariprazine
		1.5-6 mg	**6-12 mg**	**Overall**			
Extrapyramidal Symptoms	7.7%	16%	22%	17%	27%	6%	20%
Akathisia	4%	11%	14%	11%	9%	7%	16%
Restlessness	3%	4%	7%	5%	3%	3%	6%

Adverse Event	**EPS/Akathisia in Controlled Mania Studies**		**Open-label Extension Extension**
	Placebo	Cariprazine	Cariprazine
Extrapyramidal Symptoms	11%	27%	23%
Akathisia	5%	20%	32%
Restlessness	2%	6%	7%

What is striking in the schizophrenia studies is the continuing increase in new cases of akathisia over time, probably reflecting the increased levels of active moiety (cariprazine plus DDCAR) over time. This, together with a dose response relationship, is seen in all of the schizophrenia studies. It is of interest that the rates of akathisia for aripiprazole (Study MD-04) and risperidone (MD-16) appear early but do not increase much after about 2 weeks.

It appears clear that if a lower dose of 1.5 mg to 3 mg is sufficient to maintain effectiveness after the initial week, the rate of akathisia and extrapyramidal symptoms will be substantially decreased. [redacted] (b) (4), the rates of those effects appear unacceptable.

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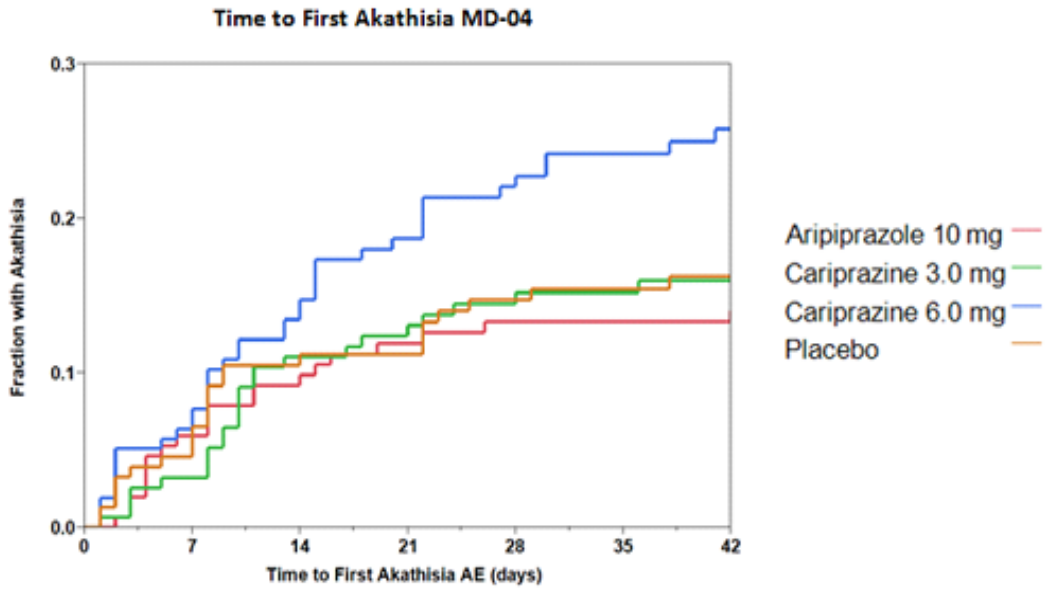

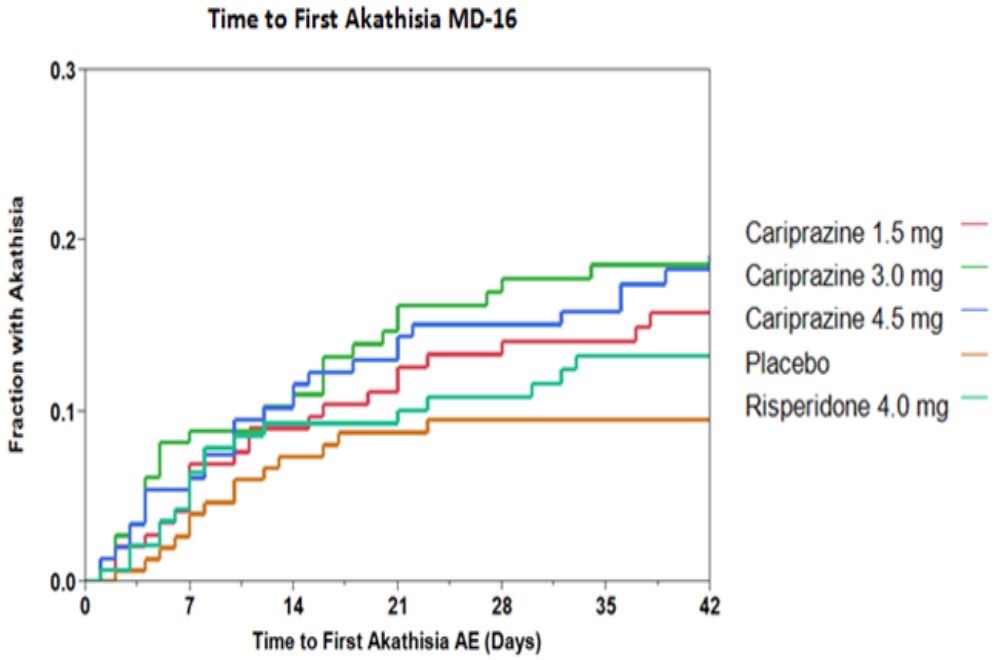

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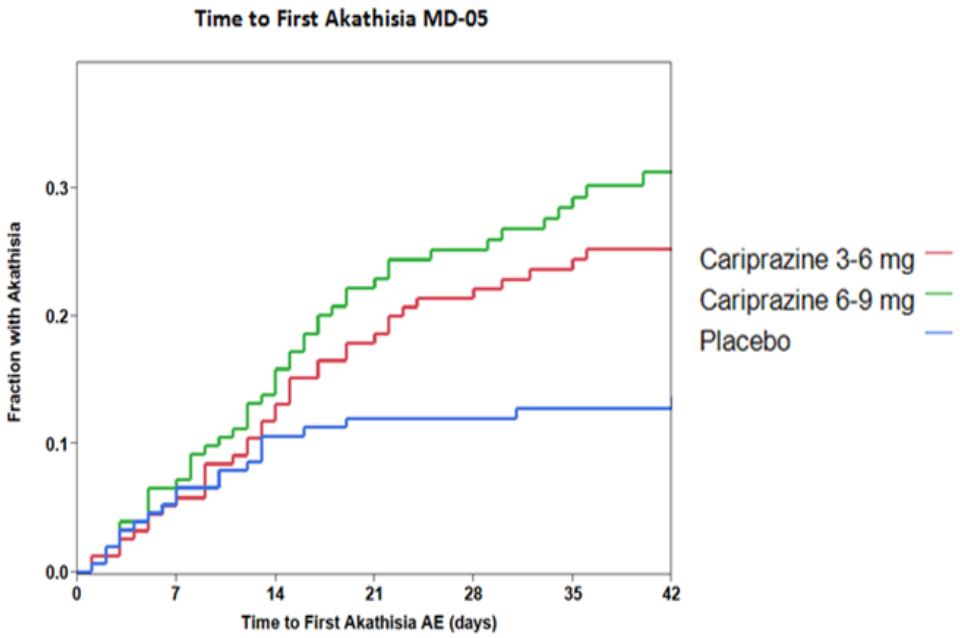

An important concern is the potential for persistence of toxicity, particularly akathisia, after discontinuation of cariprazine, given the unusually long half-life of DDCAR. Numerous cases of akathisia and other extrapyramidal symptoms were prolonged and many cases had not resolved at the last follow-up assessments, up to four weeks or more after discontinuation of cariprazine.

2. Rhabdomyolysis

There were modest dose-related CPK increases in the cariprazine groups, compared to the placebo, aripiprazole, and risperidone groups. More important, there have been 3 cases of rhabdomyolysis on cariprazine reported as clinical serious adverse events requiring hospitalization in the cariprazine clinical programs. Subject 0831125 developed rhabdomyolysis and renal failure during treatment with cariprazine 3 mg daily. Subject 0430501 was reported to have an 'acute muscle injury', with a CPK concentration of 32,280 U/L (approximately 164 times the upper limit of normal), myoglobinuria, and muscle tenderness on Day 14 during treatment with cariprazine (modal dose of 6 mg daily). Subject 0110618 developed rhabdomyolysis, with a CPK concentration of 77,820 (399 times the ULN). Rhabdomyolysis will bear further watching in subsequent studies.

3. Blood pressure elevation

Cariprazine treatment caused small dose-related elevations of systolic and diastolic blood pressure in the controlled and uncontrolled schizophrenia and mania studies; although even a modest increase in blood pressure would be important for a chronically used drug, the blood pressure effect appears dose related and the importance of this finding will depend on the dose needed. The effect is most prevalent in the 9 mg to 12 mg cariprazine group (about 2 mm Hg) with smaller effects at lower doses.

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4. Hepatotoxicity

Treatment with cariprazine was associated with some evidence of hepatocellular injury. There were substantial dose-related increases in transaminases. A higher proportion of subjects in the cariprazine group had transaminase elevations greater than 3 times, 5 times, 10 times, and 20 times the upper limit of normal, compared to the placebo group. There were no cases of transaminase elevation accompanied by elevated bilirubin with no other explanation ("Hy's Law" cases). There is thus far no evidence of serious liver injury with cariprazine, but this will bear continued watching.

5. Ocular Toxicity

We must continue to assess ocular findings in the cariprazine clinical programs. There have been cases of cataracts as well as significant Class III shifts in lens abnormalities. In addition, there were cases of retinal abnormalities and abnormalities of color vision. Although these were observed in long-term extension studies, which lacked a control group so that a causal relationship between cariprazine treatment and clinical ocular toxicity has not been established, an effect of cariprazine cannot be ruled out at this time.

There were substantial ocular toxicities in animals. In dogs, the ocular findings included cataracts, nonreversible degenerative changes in the lens, and retinal degeneration. The margins of safety for these findings were relatively low, with no-observed-effect-levels approximately 1 to 2 times the blood levels at maximum recommended human dose (b) (4) based on AUC of active moieties. Retinal degeneration also occurred in rats at exposures that provide no margin of safety at the relevant clinical exposures.

It will be necessary to continue the ophthalmologic assessments, monitor for ocular adverse events, and submit quarterly ocular summaries. You have noted that there were errors in the assessment, grading, and recording of cataracts, which you have stated may be a reason for signals of cataract development in the cariprazine program. To address these problems, ongoing and future studies should include more careful assessments, grading, and recording. The studies should include prompt review of ocular findings.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

We reserve comment on the proposed packaging configurations until the application is otherwise adequate.

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SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also

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request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.
ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT TEMPLE
11/19/2013