Walker, Diana

From: Walker, Diana
Sent: Thursday, August 07, 2008 4:58 PM
To: 'Olchaskey, Michael'
Subject: URGENT: FDA Information request/NDA 22-256/Clarification of 07Aug08 Submission (07Aug08)
Importance: High

Dear Michael,

Please refer to your NDA 22-256, Milnacipran, submission dated August 7, 2008, Resubmission of Blood Pressure Tables. The Clinical team is reviewing your submission from August 7, 2008 and has the below clarification requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than C.O.B. on Friday, August 8, 2008.

You have provided only a partial response to our August 5 clinical request. Please resubmit tables 6.3.6.1.1-1a and 6.3.6.1.2-1a such that the number and percent of patients in *each cell* of the table are indicated.

For example, with respect to SBP in the placebo group, indicate how many patients (N,%) had a SBP </= 120 at baseline, and then how many had SBP </= 120, SBP > 120-140, SBP > 140-160, and SBP > 160 at study end. Complete the tables in this way for each of the remaining placebo cells, and for each of the dose groups.

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/8/2008 01:48:49 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Thursday, August 07, 2008 2:08 PM
To: 'Olchaskey, Michael'
Subject: URGENT: FDA Information request/NDA 22-256/Clarification of 06Aug08 Submission (07Aug08)
Importance: High

Dear Michael,

Please refer to your NDA 22-256, Milnacipran, submission dated August 6, 2008, entitled "Clinical Shift Tables for Heart Rate, Laboratory Values, and ECG Parameters". The Clinical team is reviewing your submission from August 6, 2008 and has the below clarification requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than C.O.B. on Friday, August 8, 2008.

1. For Tables 2 and 3, provide the criteria for which each of the laboratory values were defined as "low," "normal," or "high."

2. Resubmit the shift analyses for the tests of liver function, using the following criteria for shifts from baseline to study end:

AST and ALT:

> 1x ULN, < 3 x ULN
>/= 3x ULN, < 5x ULN
> 5x ULN
> 10x ULN
> 20 x ULN

Bilirubin:
> 1 x ULN
> 1.5 x ULN
> 2 x ULN

Alkaline phosphatase:
> 1.5 x ULN

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/8/2008 01:35:01 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, August 06, 2008 1:49 PM
To: 'Olchaskey, Michael'
Subject: FDA Information request/NDA 22-256/Clinical (06Aug08)
Importance: High

Dear Michael,

The Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below comments and information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than C.O.B. on Monday, August 11, 2008.

The adverse event data from the placebo-controlled fibromyalgia studies show that increased blood pressure (BP) occurred more frequently in male patients taking milnacipran, compared to male patients taking placebo. Also, increased blood pressure was more frequently experienced by male milnacipran-treated patients than female milnacipran-treated patients.

To further explore these findings, conduct the following analyses (**using the placebo-controlled FM (Group 1A) data**):

1. Calculation of the mean change in BP in male vs. female patients. Also, indicate the range of BP values at the end of the study for males and females in each dose group.

2. Analysis of the hypertension status at baseline and end of study, for male vs. female patients.

3. Shift in blood pressure status (categorical change in blood pressure) from baseline to end of study, for male vs. female patients.

4. Comparison of baseline characteristics (demographics, BP, medications for HTN) for male and female patients with and without changes of clinical interest in blood pressure.

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/6/2008 02:00:45 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Tuesday, August 05, 2008 3:44 PM
To: 'Olchaskey, Michael'
Subject: FDA Information request/NDA 22-256/Clinical (05Aug08)
Importance: High

Dear Michael,

The Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Thursday, August 7, 2008**.

Resubmit the following tables and figures in the Cardiovascular-Special Topics Report, indicating - for each treatment group - the number and percent of patients in each blood pressure category at baseline, and the number and percent of patients in each blood pressure category at the end of the study.

Table 6.3.6.1.1-1 ("systolic blood pressure status at end of study by baseline status in Group 1AA")

Figure 6.3.6.1.1-1 ("systolic blood pressure: graphical representation of patient distribution at beginning and end of study")

Table 6.3.6.1.2-1 ("diastolic blood pressure status at end of study by baseline status in Group 1AA")

Figure 6.3.6.1.2-1 ("diastolic blood pressure: graphical representation of patient distribution at beginning and end of study")

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/6/2008 01:58:09 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Thursday, July 31, 2008 4:50 PM
To: 'Olchaskey, Michael'
Subject: FDA Information request/NDA 22-256/CMC (31Jul08)
Importance: High

Dear Michael:

The Chemistry, Manufacturing, and Controls (CMC) team is reviewing the proposed commercial packaging configuration for your NDA 22-256, Milnacipran, submission and has the below follow-up information request. Please provide a submission to me via FedEx (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Tuesday, August 12, 2008**. Submit the sample request below:

Provide samples of all bottles (complete, including caps) and the blister package(s)/packaging for all strengths of the product.

Please do not hesitate to contact me if you have any questions concerning this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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ON ORIGINAL

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/s/

Diana Walker
8/1/2008 09:44:21 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Wednesday, July 30, 2008 8:44 AM
To: 'Olchaskey, Michael'
Subject: FDA Clinical Information request/NDA 22-256 Milnacipran (30Jul08)

Importance: High

Dear Michael,

The Clinical team is reviewing your NDA 22-256, Milnacipran, submission and has the below comments and information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Wednesday, August 6, 2008**.

Indicate where in the NDA shift analyses and shift tables for (a) heart rate, (b) laboratory values and (c) ECG parameters are located for the controlled fibromyalgia (Group 1A) studies. **If the NDA does not contain shift analyses and shift tables, please provide them.** The analyses/tables should illustrate the incidence (number and percentage) of patients who had deviations (shifts) from normal (or varying degrees of abnormal) values at baseline, to abnormal values at study end. The figure below shows how the data should be presented:

	End of study		
Parameter/value	**Normal**	**"Abnormal value 1"**	**"Abnormal value 2"**
Baseline	**(n, %)**	**(n, %)**	**(n, %)**
Placebo			
Normal (n, %)			
"Abnormal value 1" (n, %)			
"Abnormal value2" (n, %)			
Milnacipran 100 mg/day			
Normal (n, %)			
"Abnormal value 1" (n, %)			
"Abnormal value2" (n, %)			
Milnacipran 200 mg/day			
Normal (n, %)			
"Abnormal value 1" (n, %)			
"Abnormal value2" (n, %)			

Please contact me with any questions regarding your NDA or this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/1/2008 09:43:01 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Monday, July 28, 2008 3:25 PM
To: 'Olchaskey, Michael'
Subject: FDA Information request/NDA 22-256/CMC (21Jul08)
Importance: High

Dear Michael,

I would like to send a clarification of Information request Question #5. Please forward this clarification to your review team.

The Chemistry, Manufacturing, and Controls (CMC) team is reviewing your NDA 22-256, Milnacipran, submission and has the below comments and information requests:

5. Were tablet hardness and friability evaluated as stability indicating parameters?

You may need additional time to clarify this question with your review team, as our original request specified submission by C.O.B. on Monday, July 28. Given this clarification, please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. Wednesday, July 30, 2008**.

Thank you for your assistance,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

From: Walker, Diana [mailto:Diana.Walker@fda.hhs.gov]
Sent: Monday, July 21, 2008 9:16 AM
To: Olchaskey, Michael
Cc: Parikh, Sejal
Subject: FDA Information request/NDA 22-256/CMC (21Jul08)
Importance: High

Dear Michael:

The Chemistry, Manufacturing, and Controls (CMC) team is reviewing your NDA 22-256, Milnacipran, submission and has the below comments and information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Monday, July 28, 2008**. Submit responses to the 11 (eleven) specific information requests below:

1. Provide a list of the tests performed by Forest (drug product manufacturer) on the drug substance received from Pierre Fabre Medicament (e.g. identity, appearance, etc.).

2. Provide a sample of each proposed commercial packaging configuration.

3. Clarify the differences in the manufacturing process used for the stability batches and for the proposed commercial manufacturing process.

4. Clarify whether any reprocessing is proposed during the drug product manufacturing process.

5. Provide details of any stability indicating parameter evaluations (e.g. hardness, friability, etc.).

6. Provide updated stability data on all registration batches (18 and 24 month data), given that the primary stability batches were manufactured in September 2005.

7. Provide a graphic presentation (one graph for all strengths/ batches) of the updated [ ] content stability data for drug product stored in blister packages at each storage condition (total 3 graphs). b(4)

8. Provide a graphic presentation (one graph for all strengths/ batches) of the updated [ ] content stability data for drug product stored in blister packages at each storage condition (total 3 graphs).

9. Provide a graphic presentation (one graph for all strengths/ batches) of the updated assay stability data for drug product stored in blister packages at each storage condition (total 3 graphs). b(4)

10. Provide a graph that correlates the [ ] content and the [ ] content in the drug product.

11. The limit of detection (LOD) and limit of quantitation (LOQ) for the HPLC identification and assay method (PRD-TM-ANL-00149) could not be located. Provide the LOD and LOQ for this method.

Please do not hesitate to contact me if you have any questions concerning this information request.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
8/1/2008 09:41:00 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

DISCIPLINE REVIEW LETTER

Forest Laboratories,Inc.
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, Pharm. D.
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated and received December 18, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Milnacipran HCl Tablets (12.5 mg, 25 mg, 50 mg, and 100 mg).

The Division of Biopharmaceutics has completed its review of the QT Study section of your submission, and we have the following comments and recommendations:

(1) The study was not optimally designed to assess assay sensitivity. Moxifloxacin was administered to subjects on day 1 followed by dosing with placebo or milnacipran for 37 days. The moxifloxacin arm should have been conducted concurrently with the other treatment arms in order to demonstrate that the study was designed and conducted to detect an effect on the QT/QTc interval of around 5 ms.

(2) An individual-specific heart rate correction factor (QTcNi) was derived using interval data collected at rest on day -1. This is not suitable to apply to a drug that increases heart rates outside the resting range because it assumes that the QT/RR relationship remains linear outside the resting range. According to your analysis, the mean increase in $\Delta\Delta$QTcNi is -5 (-9.4, 0.08) ms. If, however, the same analysis is performed using QTcF, the mean increase in $\Delta\Delta$QTcF is 7.7 (3.5, 12.0) ms.

(3) We recommend that you perform a repeat thorough QT study incorporating the following additional elements:

    a. Use exercise or 24-h ambulatory ECG monitoring at baseline as a method to increase the range of heart rates to compute an individual-correction factor.

b. Collect additional ECGs during the titration of milnacipran to determine the dose/concentration-response relationship for QT prolongation.

c. The moxifloxacin control should be conducted concurrently with the other arms.

d. In this study, over-encapsulation of the moxifloxacin tablet may have caused a decrease in moxifloxacin exposure. Perform blinding using a double-dummy approach.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Diana Walker, Ph.D., Regulatory Project Manager, at 301-796-4029.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
7/23/2008 11:13:52 AM

Walker, Diana

From: Walker, Diana
Sent: Wednesday, July 23, 2008 11:45 AM
To: 'Olchaskey, Michael'
Subject: RE: FDA Discipline Review Letter/NDA 22-256/Clinical(23Jul08)
Importance: High
Attachments: NDA 22-256 QT Study DR Letter.pdf

Dear Michael,

Please review the attached Discipline Review letter containing comments and recommendations regarding the QT study from your NDA 22-256 submission. You will also receive a copy of this letter through regular mail. Please contact me with any questions you have concerning this letter.

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/23/2008 03:49:46 PM
CSO

Walker, Diana

From: Walker, Diana
Sent: Monday, July 21, 2008 9:16 AM
To: 'Olchaskey, Michael'
Cc: 'Sejal.parikh@frx.com'
Subject: FDA Information request/NDA 22-256/CMC (21Jul08)
Importance: High

Dear Michael:

The Chemistry, Manufacturing, and Controls (CMC) team is reviewing your NDA 22-256, Milnacipran, submission and has the below comments and information requests. Please provide a response to me via email (followed by an official submission to your NDA) as soon as possible, but no later than **C.O.B. on Monday, July 28, 2008**. Submit responses to the 11 (eleven) specific information requests below:

1. Provide a list of the tests performed by Forest (drug product manufacturer) on the drug substance received from Pierre Fabre Medicament (e.g. identity, appearance, etc.).

2. Provide a sample of each proposed commercial packaging configuration.

3. Clarify the differences in the manufacturing process used for the stability batches and for the proposed commercial manufacturing process.

4. Clarify whether any reprocessing is proposed during the drug product manufacturing process.

5. Provide details of any stability indicating parameter evaluations (e.g. hardness, friability, etc.).

6. Provide updated stability data on all registration batches (18 and 24 month data), given that the primary stability batches were manufactured in September 2005.

7. Provide a graphic presentation (one graph for all strengths/ batches) of the updated [ ] content stability data for drug product stored in blister packages at each storage condition (total 3 graphs). b(4)

8. Provide a graphic presentation (one graph for all strengths/ batches) of the updated [ ] content stability data for drug product stored in blister packages at each storage condition (total 3 graphs).

9. Provide a graphic presentation (one graph for all strengths/ batches) of the updated assay stability data for drug product stored in blister packages at each storage condition (total 3 graphs).

10. Provide a graph that correlates the [ ] content and the [ ]' content in the drug product. b(4)

11. The limit of detection (LOD) and limit of quantitation (LOQ) for the HPLC identification and assay method (PRD-TM-ANL-00149) could not be located. Provide the LOD and LOQ for this method.

Please do not hesitate to contact me if you have any questions concerning this information request.

7/21/2008

Regards,

Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/21/2008 09:27:45 AM
CSO

Walker, Diana

From: Walker, Diana
Sent: Friday, July 11, 2008 11:26 AM
To: 'Olchaskey, Michael'
Cc: 'Sejal.parikh@frx.com'
Subject: FDA Information request/NDA 22-256/Stats (11Jul08)
Importance: High

Dear Michael:

The statistical team is reviewing your June 3, 2008, MLN02EFF.xpt submission and has the below comments and information requests for NDA 22-256. Please provide a response to me via email (followed with an official submission to your NDA) by **C.O.B. on Tuesday, July 15, 2008**. Submit responses to the comments and to the four specific information requests below:

We received MLN02EFF.xpt which was submitted on June 3, 2008. As requested, it includes the "*Last 14 days of raw 24-hour recall pain data (not imputed) in column format (i.e. PNVD71, PNVD72, ..., PNVD84)*", as well as the PNV1OB and the PNVWK15R variables. In your data definition, you explained the derivation of PNV1OB as follows:

"If patient reached 3-month landmark visit, PNV1OB is the average of valid assessments; else PNV1OB is missing."

You also explained the derivation of PNVWK15R as follows:

"PNVWK15R is the average of available assessments during week 15 if assessments >=3; otherwise is set to missing."

Suppose a patient reached the 3-month landmark (i.e. CMPLTE3M=1) and reached treatment visit 15 (TX15), the average of PNVD71 to PNVD84 should seemingly result in the value of PNV1OB. Furthermore, this average would seemingly be the same as PNVWK15R.

As an example: (Note APNDAT is the average of PNVD71 to PNVD84)

Obs	PID	ITT	CMPLTE3M	admin15	TREAT	PNVD71	PNVD72	PNVD73	PNVD74	PNVD75	PNVD76	PNVD77	PNVD78	PNVD79	PNVD80	PNVD81	PNVD82	PNVD83	PNVD84	SPVD8T	NA
1	20202	1	1	0	0	50	52	49	52	49	50	58	45	52	52	52	55	53	57	726	
2	20203	1	1	0	2	28	32	28	31	28	21	24	26	17	17	20	21	25	23	341	
3	20210	1	1	0	0	44	42	45	42	37	42	35	39	29	24	26	29	23	23	480	

Obs	PNV0CF	APNDAT	PNV1OB	PNV1CF	PNV1BF	PNVWK15R	PNVWK15B
1	50.6429	51.8571	51.8571	51.8571	51.8571	52.2857	52.2857
2	54.5714	24.3571	23.4286	23.4286	23.4286	21.2857	21.2857
3	54.7857	34.2857	40.5000	40.5000	40.5000	27.5714	27.5714

1. Patient 20202 completed the 3-month landmark and reached TX15. The APNDAT=51.8571 is equal to PNV1OB. However, this does not equal to PNVWK15R. Explain the discrepancy.

2. Patient 20203 also completed the 3-month landmark and reached TX15. The APNDAT=24.3571 which is not equal to PNV1OB. Explain this discrepancy.

3. Explain the calculation of PNV10B in each of the following scenarios:

- The subject completed the 3-month landmark and reached TX15; however, there are intermittent missing values between

PNVD71 and PNVD84 (e.g. ID=20311 or ID=20317).

- The subject completed the 3-month landmark but did not reach TX15 (classified as administratively reached Day 78), and had all the PNVD71 to PNVD84 data (e.g. ID=20707).

- The subject completed the 3-month landmark but did not reach TX15 (classified as administratively reached Day 78), and there are intermittent missing values between PNVD71 to PNVD84 (e.g. ID=21124 or ID=21132)?

- The subject completed the 3-month landmark but did not reach TX15 (classified as administratively reached Day 78), and had NO data on PNVD71 to PNVD84 (e.g. ID=29525).

4. Indicate if the explanations are applicable to Study FMS-031.

Kindly confirm receipt of this request.

Regards,
Diana

Diana L. Walker, Ph.D.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-4029
Fax: 301-796-9723/9713
Email: Diana.Walker@fda.hhs.gov

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/s/

Diana Walker
7/17/2008 08:58:37 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Friday, June 06, 2008 10:10 AM
To: 'Olchaskey, Michael'
Cc: Walker, Diana
Subject: New FDA IR/Nonclinical/NDA 22256
Importance: High

Dear Michael:

The nonclincal team has the following information request for NDA 22-256. Please provide a response to me via email (followed by an official submission to your NDA) by **COB on Tuesday, June 10th.**

b(4)

Currently, the specification for the drug product degradant [ ] exceeds the ICH Q3B(R) qualification threshold. The duration of the 28-day repeat-dose toxicology study for qualification of [ ] is inadequate for a chronic indication. If [ ]

If [ ] is not deemed a [ ], further studies may be needed to justify the safety. If it is determined that [ ] needs to be further qualified, you must submit a 90-day repeat-dose toxicology study to justify the safety, or reduce the specifications of the impurity to NMT [ ].

b(4)

Thanks,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Fax: 301-796-9723/9713
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
6/6/2008 10:12:09 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, May 28, 2008 12:31 PM
To: 'Olchaskey, Michael'
Cc: Walker, Diana
Subject: FDA IR/NDA 22256/Stats (28May08)
Importance: High

Dear Michael:

The clinical/statistical team has the below information requests for NDA 22-256. Please provide a response to me via email (followed with an official submission to your NDA) by **C.O.B. on Monday, June 2, 2008**. Kindly confirm receipt of this request.

1. Clarify whether you are using the two-step approach from Study MLN-MD-02 or the stepdown approach (i.e. eight primary comparisons) presented in Vol. 1, page 60 of the FMS-031 study report to control the overall experiment-wise error rate in Study FMS-031 under the Unified Program Analysis.

2. In the Clinical Study Report for MLN-MD-02, Vol. 2, pages 3 – 9, you presented tables on the patient disposition by study visit. At the 3-month endpoint (Tx15), it appears that close to 70% completed the study. However, only 80% of these completers reached visit Tx15. You stated that the majority of those who did not reach visit Tx15 were "Administratively Completed at 3-months" while some were "completers at Day 78". Provide further details explaining "Administratively Completed at 3-months" and "completers at Day 78".

3. Explain the derivation of PNV1OB and PNV1CF (in d_resp.xpt) including how the results from ped.xpt are used in the derivation of these variables.

4. Clarify how the number of days of rescue (i.e. variable "ND1") from d_resp.xpt is derived given data from d_rscu.xpt. Also, include an explanation of the derivation of N1CF, N1OB, and PN15CF

5. For each study, provide a new dataset with the following variables:

   a. Patient ID
   b. Treatment arm
   c. ITT/Safety Population flag
   d. Completer at 3 months (yes/no)
   e. Reason for discontinuation
   f. a flag indicating whether the value is an imputed (i.e. LOCF) value or the actual value coinciding with PNV1CF
   g. Last 14 days of raw "24-hour recall pain" data (not imputed) in column format (i.e. PNVD70, PNVD71, …, PNVD84)
   h. PNVWK14L – average '24-hour recall pain' at Week 14. The result should match Table 14.4.3.1.1A of Study MLN-MD-02 and Table 14.4.2.2.1 of Study FMS-031 based on LOCF imputation. In addition, the result should match the Week 14 data from ped.xpt.
   i. PNVWK15L – average '24-hour recall pain' at Week 15. The result should match Table 14.4.3.1.1A of Study MLN-MD-02 and Table 14.4.2.2.1 of Study FMS-031 based on LOCF imputation. In addition, the result should match the Week 15 data from ped.xpt.

j. PNVWK14R based on raw data (no imputation)
k. PNVWK15R based on raw data (no imputation)
l. PNVWK14B based on BOCF imputation
m. PNVWK15B based on BOCF imputation
n. PNV0CF
o. PNV1OB
p. PNV1CF
q. PNV1BF – new variable for BOCF imputation
r. PGV1CF
s. PGV1OB
t. PG15CF
u. PG15OB
v. PG15S1
w. ND1
x. N1OB
y. N1CF
z. PN15CF
aa. PN15S1

Regards,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Fax: 301-796-9723/9713
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
5/28/2008 12:33:44 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Tuesday, May 27, 2008 2:50 PM
To: 'Olchaskey, Michael'
Cc: Walker, Diana
Subject: New FDA IR_CMC_NDA 22256 (27May08)
Importance: High

Dear Michael:

The review team has the below information request for NDA 22-256:

Provide copies of the Certificates of Analyses (CoAs) for the drug substance batches [ ]-003, [ ]-006, and [ ]/174. b(4)

Please respond to me via email (followed with an official submission to your NDA) at your earliest convenience; however, no later than C.O.B. on Thursday, May 29th.

Kindly confirm receipt of this request.

Hope you are doing well and had a nice holiday!

Thanks,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Fax: 301-796-9723/9713
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
5/27/2008 02:53:55 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

INFORMATION REQUEST LETTER

5/20/08

Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, CA 92121

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your December 18, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Milnacripan hydrochloride, tablets.

We are reviewing the label provided in your submission for adherence to the format proposed by the Physician's Labeling Rule. Provided below is a list of comments based upon Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review Divisions. We request a prompt written response in order to continue our evaluation of your NDA.

The following issues/deficiencies have been identified in your proposed labeling.

Highlights

b(4)

Tablet of Contents

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Full Prescribing Information (FPI)

1. [redacted] b(4)

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at 301-796-2246.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/20/2008 02:40:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

INFORMATION REQUEST LETTER

5/9/08

Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your December 18, 2007, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Milnacipran hydrochloride oral tablets.

We are reviewing the label provided in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

The following issues/deficiencies have been identified by the Division of Drug Marketing, Advertising and Communications (DDMAC) in your proposed labeling:

Highlights

Boxed Warning

[

b(4)

]

Indications and Usage

[

b(4)

]

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Carton and Container Labeling

b(4)

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
5/9/2008 11:28:28 AM

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Tuesday, April 08, 2008 6:21 PM
To: 'Olchaskey, Michael'
Subject: New IR/Clinical/NDA 22256/8April08
Importance: High

Dear Michael:

The Clinical Team has the following information requests for NDA 22-256:

Please provide a dataset that includes all patients from the fibromyalgia studies FMS031 and MLN-MD-02 who had protocol violations. The dataset should include the following variables (in the same format and coding that was used for the ISS datasets):

Unique subject identifier number

Protocol number

Site number

ICH category (class) of protocol violation

Variable/flag indicating whether the patient was discontinued due to a protocol violation

Please provide a response to me via email followed by an official submission to your NDA by **C.O.B. on April 15, 2008**.

Kindly confirm receipt of this request.

Best,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
4/8/2008 06:26:08 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Monday, April 07, 2008 2:36 PM
To: 'Olchaskey, Michael'
Subject: IR/N 22256/7April08
Importance: High

Dear Michael:

Subsequent to our April 3, 2008, information request, the review team has requested an additional clarification:

Regarding your submitted ——— , there seems to be two, — labeling submissions (one is a patient start kit and the other is a starter pack). Clarify the difference. b(4)

Please include your response as part of the previously requested April 11, 2008, response material. Kindly confirm receipt of this request.

Best,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
4/7/2008 03:04:45 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Thursday, April 03, 2008 11:09 AM
To: 'Olchaskey, Michael'
Subject: New IR/N 22256/03April08
Importance: High

Dear Michael:

The review team has the following information requests for N 22-256:

1. Provide a "working sample" of the [ ] patient starter pack. b(4)

2. Provide a sample of the actual configuration of the blister card for the ten-count sample box.

3. Provide a sample of the carton labeling of the 60- and [ ] count bottles. b(4)

Please provide a response to me via email followed by an official submission to your NDA by Friday, April 11, 2008, if possible. Kindly confirm receipt of this request.

Regards,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
4/3/2008 11:12:19 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Monday, March 31, 2008 9:20 AM
To: Olchaskey, Michael
Subject: FDA Response to CPharm Submission/NDA 22256
Importance: High

Dear Michael:

Reference is made to your March 17, 2008, clinical pharmacology submission to NDA 22-256. You have requested to confirm the projected timing of the submission of the final study report. As requested by the review team, please submit the final study report ***on or before July 3, 2008***.

Kindly confirm receipt of this request.

Best Regards,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
3/31/2008 09:23:17 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, March 19, 2008 8:22 AM
To: 'Olchaskey, Michael'
Subject: FDA Comments/120 Sfty Update Proposal
Importance: High

Dear Michael:

The review team has the following comments regarding your January 30, 2008, submission to NDA 22-256:

We note your January 30th proposal regarding the proposed 120-day Safety Update, to include new information from recent PK studies, ongoing clinical studies, and foreign post-marketing safety reports.

The Safety Update discussions should compare the original safety data and the safety update data. The Safety Update should include discussions of patient exposure, disposition, adverse events, as well as discussions of lab, ECG, and vital signs. Adverse event discussion should include information about deaths, SAEs, and adverse events leading to discontinuation.

The tabular summaries in the Safety Update should display the information from the initial NDA submission ("old data"), information from the new subjects ("new data"), and the updated cumulative data for the combined population (old and new subject data).

Kindly confirm receipt of this email. Should you have concerns/questions, please contact me.

Best,
Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
3/19/2008 08:24:45 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-256

INFORMATION REQUEST LETTER

3/3/08

Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Milnacipran hydrochloride oral tablets.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical Pharmacology:

We noted that you have not conducted *in vitro* studies using human hepatocytes to investigate the potential of enzyme induction with milnacipran. This is a critical piece of information for the full assessment of the drug-drug interaction potential of milnacipran with other co-administered drugs. Therefore, you are advised to assess all available data to determine if the induction potential can be obtained from existing data and/or conduct *in vitro* induction study(s).

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
3/3/2008 09:09:08 AM

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Friday, February 22, 2008 3:46 PM
To: 'Olchaskey, Michael'
Subject: Info.Request/NDA 22256/Drug Abuse & Dependence/22Feb08
Importance: High

Dear Michael:

The review team has the following information request for NDA 22-256:

Clarify where we can find the Drug Abuse and Dependence section for your application.

Please respond to me via email (followed by an official submission) by C.O.B. on Monday, February 25, 2008, if possible.

Regards,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
2/22/2008 03:55:26 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-256

2/20/08

Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated December 18, 2007, received December 18, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Milnacipran hydrochloride oral tablets, 12.5-, 25-, 50- and 100-mg.

We also refer to your submissions dated January 4, 5, 21, and 30, 2008.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is October 18, 2008.

During our filing review of your application, we identified the following potential review issues and request that you submit the following information:

1. Provide confirmation that all sites are ready for cGMP inspection.

2. Provide statistical analysis of the stability test data in SAS format during the early stage of the review cycle.

3. Provide a master (blank) batch record for the [ ] of the 12.5-mg and 100-mg tablets and selected representative executed batch records. If provided in the NDA, identify the Module and Section of the NDA that includes the bath records.

b(4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on September 11, 2007, for the pediatric study requirement for this application for all pediatric patients until adequate safety and efficacy have been demonstrated in the adult population.

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia
And Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sharon Hertz
2/20/2008 01:01:50 PM
Signing for Bob Rappaport, M.D.

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Tuesday, February 12, 2008 11:03 AM
To: 'Olchaskey, Michael'
Subject: Info.Request/QT SAS Codes/NDA 22256/12Feb08
Importance: High

Dear Michael:

Unfortunately, the SAS codes that you submitted are not related to the QT Study MLN-PK-10 but, to other studies. Please provide the SAS Codes related to the QT Study MLN-PK-10 at your earliest convenience.

Kindly confirm receipt of this request.

Thanks,

Lauren

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/s/

Lauren Tornetta
2/13/2008 01:32:49 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, February 06, 2008 1:27 PM
To: 'Olchaskey, Michael'
Subject: #2 Info.Request/NDA 22256/06Feb08
Importance: High

Hi Michael:

The team has notified me of this additional information request for NDA 22-256:

Submit the SAS codes for the primary analysis.

As previously relayed, please submit this information to me via email (followed by an official submission to your NDA) by COB on Feb. 8th (Friday).

Thanks,

Lauren

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/s/

Lauren Tornetta
2/6/2008 01:30:28 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, February 06, 2008 8:08 AM
To: 'Olchaskey, Michael'
Subject: Info.Requests/NDA 22-256/06Feb08
Importance: High
Attachments: HighlightsofClinicalPharmacology.doc

Dear Michael,

The Division has the following information requests for NDA 22-256:

1. Complete the attached ClinPharm table and submit **as soon as possible**.
2. Submit a copy of the most recent Investigator's Brochure for this application.

3. The team noticed that you have not submitted ECGs to the ECG Warehouse. Submit all related ECG waveforms to the www.ecgwarehouse.com

Provide responses to the above requests to me via email (followed by official submissions to your NDA) at your earliest convenience; however, no later than C.O.B., February 8, 2008, if possible.

Kindly confirm receipt of this email.

Best,

Lauren P. Tornetta, M.S., M.B.A.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events: dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route: percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.

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/s/

Lauren Tornetta
2/6/2008 08:14:31 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Thursday, January 17, 2008 1:31 PM
To: 'Michael.Olchaskey@frx.com'
Subject: FDA Request/CMC/N 22256
Importance: High

Dear Michael:

The chemistry team has the following information request for NDA 22-256.

Provide the complete name and contact information (including phone numbers) for your foreign facilities including:

1. Pierre Fabre Medicament, Plantes & Indistrie, 16 rue Gaillac Cedex, FRANCE, the drug substance manufacturer

2. Forest Laboratories, Ireland, LTD, Clonshauch Industrial Estate, Clonshauch, Dublin 17, Ireland, the drug product manufacturer

Please provide this information to me via email, followed by an official submission to your NDA by COB on Friday, January 18, 2008, if possible.

Kindly confirm receipt of this request.

Regards,

Lauren P. Tornetta, M.S.
Regulatory Project Manager
FDA/CDER/ODE II/DAARP
Tel: 301-796-2246
Email: Lauren.Tornetta@fda.hhs.gov

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/s/

Lauren Tornetta
1/17/2008 01:34:58 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-256

NDA ACKNOWLEDGMENT

Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, CA 92121

1/14/08

Attention: Michael K. Olchaskey, PharmD
Director, Regulatory Affairs

Dear Dr. Olchaskey:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Milnacipran HCL

Dosage Form: Oral Tablets

Strengths: 12.5-, 25-, 50-, and 100-mg

Date of Application: December 18, 2007

Date of Receipt: December 18, 2007

Our Reference Number: NDA 22-256

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 15, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
1/14/2008 09:53:43 AM

MEMORANDUM OF TELECON

DATE: February 11, 2008

APPLICATION NUMBER: NDA 22-256

BETWEEN: Forest Laboratories, Inc. authorized agent for Cypress Bioscience, Inc.

Name: **Cypress Bioscience, Inc.**

R. Michael Gendreau, MD, PhD – Vice President, Clinical Development & Chief Medical Officer
Ciara Kennedy, PhD, MBA – Senior Director, Business Development

Forest Laboratories, Inc.

Robert Jackson, MBA – Vice President, Regulatory Affairs
Michael Olchaskey, PharmD – Director, Regulatory Affairs
Ivan Gergel, MD – Senior Vice President, Scientific Affairs & President, Forest Research Institute
Marco Taglietti, MD – Executive Vice President, Forest Research Institute & Chief Medical Officer
Neil Shusterman, MD – Senior Vice President, Clinical Development
James Perhach, PhD – Executive Director, Clinical Development
Robert Palmer, MD – Senior Director, Clinical Development
John Castellana, PhD – Senior Vice President, Clinical Operations & Biometrics
Hongjie Zheng, PhD – Executive Director, Biostatistics
Roger Qu, PhD – Senior Director, Biostatistics

Phone: 1-800-411-0160/Passcode: 174998

AND

Name: Sharon Hertz, M.S.; Mwango Kashoki, M.D., M.P.H.; Jane Filie, M.D.; Lauren Tornetta, M.S., M.B.A.
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

SUBJECT: Review Classification and Fibromyalgia Indication

In a teleconference held on February 11, 2008, Dr. Hertz informed the Sponsor on the Division's current thinking on developing products to treat fibromyalgia. The Division has limited the indication to "treatment of fibromyalgia" and is no longer recognizing two different indications (i.e., treatment of pain and treatment of the syndrome). A Sponsor must complete two successful studies with a validated pain scale as the primary endpoint in order to support this indication. The trials should be at least three months in duration. In addition, Sponsors should study other domains as secondary outcomes such as sleep, fatigue, and function. If the product is determined to be effective

in any of these domains, information can be added to the Clinical Trials section of the label and the Sponsor may be able to utilize this information in their marketing endeavors. The Division also believes that the Fibromyalgia Impact Questionnaire (FIQ) may not be as advantageous as previously thought. Therefore, the Division will accept the physical function subscale of the Short-Form 36 Health Questionnaire (SF36) as a measure of function.

Dr. Hertz acknowledged that the Sponsor was advanced in their program and agreed that their three component primary endpoints were an acceptable approach. Dr. Hertz stated that the Division would be willing to accept revised draft product labeling at this time. Dr. Hertz indicated that even if the Sponsor had not met their goals on the triple composite endpoint, the Agency would have been willing to review the package based on the revised criteria.

Dr. Hertz clarified that the "treatment of fibromyalgia" indication is not intended to be distinct from the current label for Lyrica, which has a "management of fibromyalgia" indication.

Dr. Hertz stated that NDA 22-256 would not be eligible for priority review; but, rather a standard 10-month review classification.

Lauren Tornetta, M.S., M.B.A.
Regulatory Project Manager

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/s/

Lauren Tornetta
2/28/2008 01:40:00 PM
CSO

10/14/08

MEMORANDUM

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

DATE: October 7, 2008

TO: File

FROM: Diana L. Walker, PhD, Regulatory Project Manager

SUBJECT: **Pre-Approval Safety Conference**
NDA 22-256, Savella (Milnacipran HCl), 12.5 mg, 25 mg, 50 mg, and 100 mg Tablets

In lieu of a separately scheduled preapproval safety conference with OSE staff, the Division chose to include OSE staff in the planned review division meeting. OSE staff members were invited, and attended, the Wrap-Up meeting for NDA 22-256, Savella, on September 4, 2008. Members of OSE staff present at the meeting were Chris Wheeler, Regulatory Project Manager, and Lauren Lee (Choi), Lead Pharmacist. Also present were the following: Denise Baugh and Linda Kim-Jung, Bob Rappaport, Sharon Hertz, Mwango Kashoki, Jane Filie, Kit Bonson, Dionne price, Joan Buenconsejo, Dan Mellon, Asoke Mukherjee, Elsbeth Chikhale, Suresh Doddapaneni, Sam Al Habet, Leah Ripper, Sharon Turner-Rinehardt, Jessica Benjamin, and Curt Rosebraugh (via telephone).

During the meeting, the Medical Officer/Clinical reviewer gave a comprehensive overview of the clinical studies, adverse events, safety concerns, and potential post-marketing requirements. The Medical Officer's comprehensive review was forwarded to the OSE staff after the meeting, care of Lauren Lee (Choi).

OSE was asked to comment on pre-approval safety issues for milnacipran (NDA 22256). They responded with the following: "The only information that DPV-II has available for which DAARP has not specifically commented on are 161 foreign reports received in AERS from 1997 to 2008. Based upon crude count analysis of these reports, the profile of events reported does not appear to be different than what is expected of the SSRI/NSRI drug class of which milnaciprin is a member. These 161 reports should be a *subset* of the 1496 foreign postmarketing reports that the sponsor submitted as part of the NDA, which are mentioned in DAARP's Milnaciprin's Clinical Review (Section 7.2.2.2).

In considering the 161 reports (mentioned above), DPV-II finds no safety concerns that would necessitate anything beyond standard post-market safety monitoring and reporting."

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/s/

Diana Walker
10/14/2008 09:45:07 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	March 16, 2007
TIME:	3:00 p.m. – 4:00 p.m. (EST)
LOCATION:	CDER White Oak Conference Room 1309, Bldg. 22
APPLICATION:	IND 63,736
PRODUCT:	Milnacipran Hydrochloride
INDICATION:	Fibromyalgia Syndrome
SPONSOR:	Forest Laboratories
TYPE OF MEETING:	B/Pre-NDA
MEETING CHAIR:	Mwango Kashoki, M.D., Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
MEETING RECORDER:	Lauren Tornetta, M.S., Regulatory Project Manager

FDA Attendees	Title
Bob Rappaport, M.D.	Director, DAARP
Sharon Hertz, M.D.	Deputy Director, DAARP
Ali Al-Hakim, Ph.D.	Pharmaceutical Assessment Lead
Sally Choe, Ph.D.	Clinical Pharmacology Reviewer
Mwango Kashoki, M.D., M.P.H.	Medical Team Leader
Anjelina Pokrovnichka, M.D.	Medical Officer
Dionne Price, Ph.D.	Statistical Team Leader
Joan Buenconsejo, Ph.D.	Statistical Reviewer
Mary Dempsey	Office of Surveillance and Epidemiology
Suzanne Berkman	Office of Surveillance and Epidemiology
Lauren Tornetta, M.S.	Regulatory Project Manager
Sponsor Attendees	**Title**
R. Michael Gendreau, M.D., Ph.D.	Clinical Development, **Cypress Bioscience, Inc.**
Theresa Fico, Ph.D.	Project Management, **Forest Laboratories, Inc.**
Michael Olchaskey, PharmD	Regulatory Affairs, **Forest Laboratories, Inc.**
Robert Palmer, M.D.	Clinical Development, **Forest Laboratories, Inc.**
James Perhach, Ph.D.	Clinical Development, **Forest Laboratories, Inc.**
Neil Shusterman, M.D.	Clinical Development, **Forest Laboratories, Inc.**
Hongjie Zheng, Ph.D.	Biostatistics, **Forest Laboratories, Inc.**
Peng (Roger) Qu, Ph.D.	Biostatistics, **Forest Laboratories, Inc.**
Oliver Vitton, M.D.	Project Management, **Pierre Fabre Medicament**
[ ]	[ ] **Consultant**
[ ]	[ ] **Consultant**
[ ]	[ ] **Consultant**
[ ]	[ ] **Consultant**
Sejal A. Parikh, PharmD	Post Doctoral Fellow, **Forest Research Institute**

b(4)

BACKGROUND:

Reference is made to the Industry meeting held on June 2, 20006, the Information Amendment and Request for Feedback submitted to IND 63,736 on August 23, 2006 (serial #180), and the Request for a Type C meeting (serial #190) submitted to IND 63,736 on October 20, 2006.

MEETING OBJECTIVES:

1. To discuss the adequacy and presentation of the data for the NDA, to be submitted as an eCTD.

2. To resolve any outstanding issues concerning:

    a. The previously submitted SAP for MLN-MD-02, an ongoing pivotal study for which the last patient, last visit occurred on December 18, 2006.

    b. The validation of the SF-36 PCS as the outcome measure for the Physical Function component of the responder definition for the fibromyalgia syndrome indication that has been previously defined by the Division.

3. To acquaint reviewers with the range of information to be included in the application.

ACTION ITEM:

Division to clarify the mandatory requirements regarding the number of primary system organ class (SOC) variables.

DISCUSSION POINTS:

The Sponsor's questions are presented below in *italicized* text. Agency responses, prepared and forwarded to the Sponsor prior to the meeting, are **bolded.** Following introductions, the discussion focused on Questions 1 and 3, and the "Additional Comments and Clarifications" section. Discussion related to these questions is presented in normal text.

Question 1. We propose to use the primary analysis method and population specified in the protocol and SAP for Study MLN-MD-02 as the statistical methodology for performing pooled efficacy analysis of Studies FMS031 and MLN-MD-02 in the Integrated Summary of Efficacy (ISE). Does the FDA concur with this approach?

[Study MLN-MD-02 excluded patients with a Beck Depression Inventory (BDI) score > 25, measured physical function using the Short Form 36 – Physical Component Scale (SF-36 PCS), and imputed missing data using the baseline observation carried forward (BOCF) method.]

FDA Response:

The main purpose of the integrated summary of efficacy is to explain how the results of the individual studies support the claims being made. Although required analyses by age, sex and race are often best conducted on the pooled data, a pooled analysis of individual studies is not usually very helpful in achieving the goal of the ISE. However, in the case of conflicting results, a statistical meta-analysis of the studies may be appropriate.

Discussion:

The Sponsor provided a schematic summarizing the development program for Milnacipran as a treatment of fibromyalgia, and gave an overview of the key milestones and important changes in the development plan as based on advice received from the Agency. Specifically, the Agency has advised the Sponsor on the number of pivotal trials required for a fibromyalgia indication, the duration of the trials, primary end-points and efficacy analyses, imputation methods for missing data, and instruments to measure physical function.

Agreement was reached between the Sponsor and the Agency that two indications are possible for Milnacipran: treatment of the pain of fibromyalgia, or treatment of fibromyalgia syndrome. Also, a trial length of 3 months is adequate, BOCF is an acceptable imputation method, and the SF-36 PCS can be used as a measure of physical function. The Sponsor was also informed that Continuous Responder Analyses are recommended but not required.

The Sponsor stated that they are seeking a "treatment of fibromyalgia syndrome indication," and requested further clarification on the Division's requirements for this indication. The Sponsor stated that to support this indication, they will submit the results of study FMS031 as based on the pre-specified statistical analysis plan (SAP). In this SAP, the Fibromyalgia Impairment Questionnaire – Physical Function (FIQ-PF) scale was used to measure physical function, and patients with depression, as measured by the Mini International Neuropsychiatric Interview (MINI) scale, were excluded from the analysis. Also, the Sponsor will provide the results of study MLN-MD-02 which used the SF-36 PCS to measure function, and excluded patients with depression, as assessed by the Beck Depression Inventory (BDI). Finally, the Sponsor will submit an integrated (pooled) efficacy analysis of studies FMS031 and MLN-MD-02, using the primary analysis method and population specified for study MLN-MD-02. The Sponsor assumes that the patient selection criteria and SAP for MLN-MD-02 are more appropriate for detection of an effect than those used in FMS031; therefore the integrated analysis will provide additional evidence of efficacy under "ideal" conditions.

The Sponsor also described plans to re-analyze study FMS031 using the analysis methods of MLN-MD-02. The Sponsor confirmed that both the SF-36 PCS and the BDI were used during the trial as a secondary efficacy measures.

Dr. Rappaport stated the Sponsor's proposal for evaluation of efficacy is acceptable.

Dr. Hertz inquired about the Sponsor's findings upon re-analyses of Study FMS031 using the MLN-MD-02 criteria and imputation with BOCF. The Sponsor stated that imputation using both BOCF and last observation carried forward (LOCF) were positive with respect to the pain endpoint, and suggest efficacy to support an indication of treatment of fibromyalgia syndrome (i.e. positive results for pain, function, and patient global endpoints).

Question 2. Given the various sources of safety information, does the FDA concur with the proposed method of grouping the studies and presenting the safety data?

- *Core safety data (GCP studies in normal volunteers and patients with fibromyalgia)*
- *Supporting safety data (GCP, placebo-controlled studies in non-fibromyalgia patients)*
- *Historical safety data (data from 43 Phase 2/3, GCP and non-GCP studies in the 1997 European Marketing Authorization Application (MAA) for major depressive disorder)*
- *Postmarketing experience (postmarketing studies in non-fibromyalgia patients and spontaneous adverse event reports)*

FDA Response:

1. **In general, your proposal for grouping the safety studies and for presentation of the safety data is acceptable. For the core safety data (trials in normal volunteers and fibromyalgia patients), provide separate safety summary tables for the clinical pharmacology trials and the Phase 2/3 studies in fibromyalgia.**

2. **Include a summary of the post-marketing experience with milnacipran, and discuss post-marketing adverse events that have resulted in label changes.**

Discussion: No further discussion for Question 2.

Question 3. Specifically, given the nature of the Historical Safety Data originally submitted in Europe for the MAA, we plan to provide the Safety Summary from the 1997 MAA and further summarize these data by providing deaths and SAEs as line listings. Does the FDA concur with the plans for summarizing the safety data from the 1997 Pierre Fabre MAA for MDD in the current submission?

FDA Response:

1. **Provision of a summary of the MDD studies submitted for the MAA is acceptable. The summary should present information by:**

    a. **Good Clinical Practice (GCP) vs. non-GCP studies**

    b. **Controlled vs. uncontrolled studies**

Discussion:

The Sponsor stated that they intend to submit the existing MAA summary, and will also submit a supplement in which results for the GCP, non-GCP, controlled, and uncontrolled trials will be described. The Division responded that this was acceptable.

Question 4: We propose to structure the Integrated Summary of Safety (ISS) according to the format specified for the Summary of Clinical Safety in Module 2 of the Common Technical Document (CTD). We then anticipate using the same document, expected to be less than 400 pages, for both purposes by including it in Module 5 and referring to it in Module 2. A draft table of contents for the proposed document is included in Appendix II. Is this approach acceptable to the FDA?

FDA Response:

1. **The ISS must meet the requirements specified in the 21CFR 314.5(d)(5), and should follow FDA guidance regarding summarization of clinical and statistical data, (see Guideline for the Format and Content of the Clinical and Statistical Sections of an Application).**

2. **The limits on size for Module 2 of the CTD may prevent you from meeting these requirements. This section is intended for a true summary, Module 5 in intended for integrated analyses of data across studies. Section 5.3.5.3 of Module 5 does not confer such restrictions. Therefore, the Division recommends that you include all analyses and summaries that would typically be a part of the ISS in this section.**

Discussion: No further discussion for Question 4.

Question 5: Does the FDA concur that studies in patients younger than 18 years can be deferred until there is better agreement on the definition of the syndrome in children and appropriate instruments for measuring physical function can be identified and validated for children?

FDA Response:

Pediatric studies may be deferred until after approval in adults.

Discussion: No further discussion for Question 5.

Question 6: We believe that milnacipran for the treatment of fibromyalgia meets the criteria for priority review, as set forth in Center for Drug Evaluation and Research Manual of Policies and Procedures 6020.3. Does the FDA concur?

FDA Response:

1. **We agree that an application for the treatment of fibromyalgia merits consideration for priority review.**

2. **Designation of review status (priority vs. standard) will be made at the time of NDA submission.**

Discussion: No further discussion for Question 6.

Comments from the Office of Surveillance and Epidemiology (OSE):

1. **If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).**

2. **For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:**

   Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

   Development and Use of Risk Minimization Action Plans: http://www.fda.gov/cder/guidance/6358fnl.htm>

   Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment: http://www.fda.gov/cder/guidance/6359OCC.htm

3. **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**

4. **The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

Additional FDA Comments:

A. Provide a Pre-NDA CMC package and request a subsequent meeting to discuss the development plan prior to submission of the NDA.

B. The Division requests the following for the submitted datasets:

1. **The integrated safety dataset that should include the following fields/variables:**
   - **A unique patient identifier**
   - **Study/protocol number**
   - **Patient's treatment assignment**
   - **Demographic characteristics, including gender, chronological age (not date of birth), and race**
   - **Dosing at time of adverse event**
   - **Dosing prior to event (if different)**
   - **Duration of event (or start and stop dates)**
   - **Days on study drug at time of event**
   - **Outcome of event (e.g. ongoing, resolved, led to discontinuation)**
   - **Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).**
   - **Marker for serious adverse events**
   - **Verbatim term**

2. **The adverse event dataset should include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset should also include the Verbatim term taken from the case report form.**

3. **Please see the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables should appear and does not address other content that is usually contained in the adverse event data set.**

4. **In the adverse event data set, please provide a variable that gives the numeric MedDRA code for each lower level term.**

5. **The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to**

another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

6. **Please provide a detailed description for how verbatim terms were coded to lower level terms according to the ICH MedDRA Term Selection: Points to Consider document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.**

7. **Please provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.**

8. **The spelling and capitalization of MedDRA terms should match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.**

9. **Also, for the concomitant medication dataset, you should use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.**

10. **For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result should be in numeric format.**

11. **Please perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.**

12. **In every dataset, all dates should be formatted as ISO date format.**

13. **Across all datasets, the same coding should be used for common variables, e.g. "PBO" for the placebo group. Datasets should not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable should be included in the datasets.**

14. **All datasets should contain the following variables/fields (in the same format and coding):**
    - **Each subject should have one unique ID across the entire NDA**
    - **Study number**
    - **Treatment assignment**
    - **Demographic characteristics (age, race, gender, etc.)**

C. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups are not sufficient without ready identification of the specific patients with such abnormalities.

D. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

Discussion related to the "Additional Comments" Section:

1. The Sponsor asked if the "treatment of fibromyalgia syndrome" indication would warrant an Advisory Committee Meeting. Dr. Hertz stated that, barring an unforeseen controversy, an Advisory Committee Meeting was not indicated.

2. The Sponsor acknowledged the Division's request for a separate, chemistry related meeting. Dr. Al-Hakim stated that the Division would like to review the Sponsor's chemistry development program prior to the NDA submission and asked the Sponsor when they plan to submit the application. The Sponsor stated that they plan to submit the NDA by the end of this year.

3. The Sponsor stated their intention to submit the NDA in e-CTD format and asked whether it was possible to meet with the Division, prior to NDA submission, to review how the data will be presented and linked in the NDA submission. Dr. Kashoki agreed.

4. Regarding the mock adverse event dataset that the Division provided, the Sponsor asked if inclusion of two, primary system organ class (SOC) variables is mandatory, since they only have one. Dr. Kashoki stated that the Division would seek clarification from Agency's experts in MedDRA.

   Post-meeting note:
   MedDRA is characterized by multiaxiality; that is, a preferred term (PT) can be assigned to more than one SOC. In these instances, one SOC will be primary, and the others secondary. For example, dyspnea is represented in two SOCs: "respiratory, thoracic, and mediastinal disorders" (primary), and "cardiac disorders" (secondary).

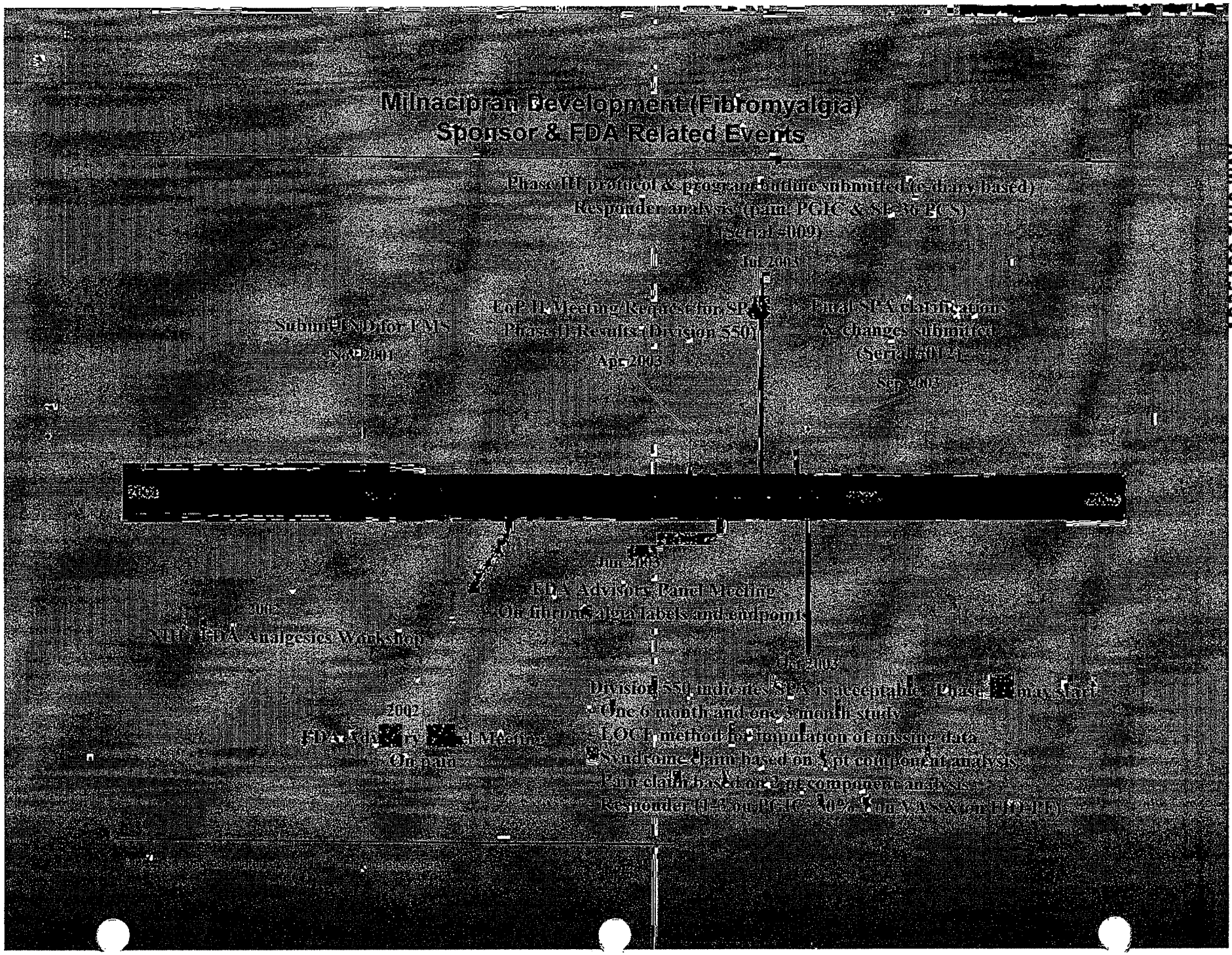
   Ensure that every PT is coded to all appropriate SOCs. Note that the following three SOCs do not have multiaxial assignments for any of their terms (i.e. terms assigned to these SOCs do not appear in any other SOC):

SOC *Investigations*
SOC *Surgical and medical procedures*
SOC *Social circumstances*

Note also that the example data set that was provided contained an error: the Preferred Term and the High Level Term variables were placed in the same column; they should be separate variables each with their own column. A corrected table is included in the meeting minutes.

HANDOUTS:

The Sponsor provided a timeline entitled, *"Milnacipran Development (Fibromyalgia) Sponsor & FDA Related Events"* of key events/milestones of their development program.



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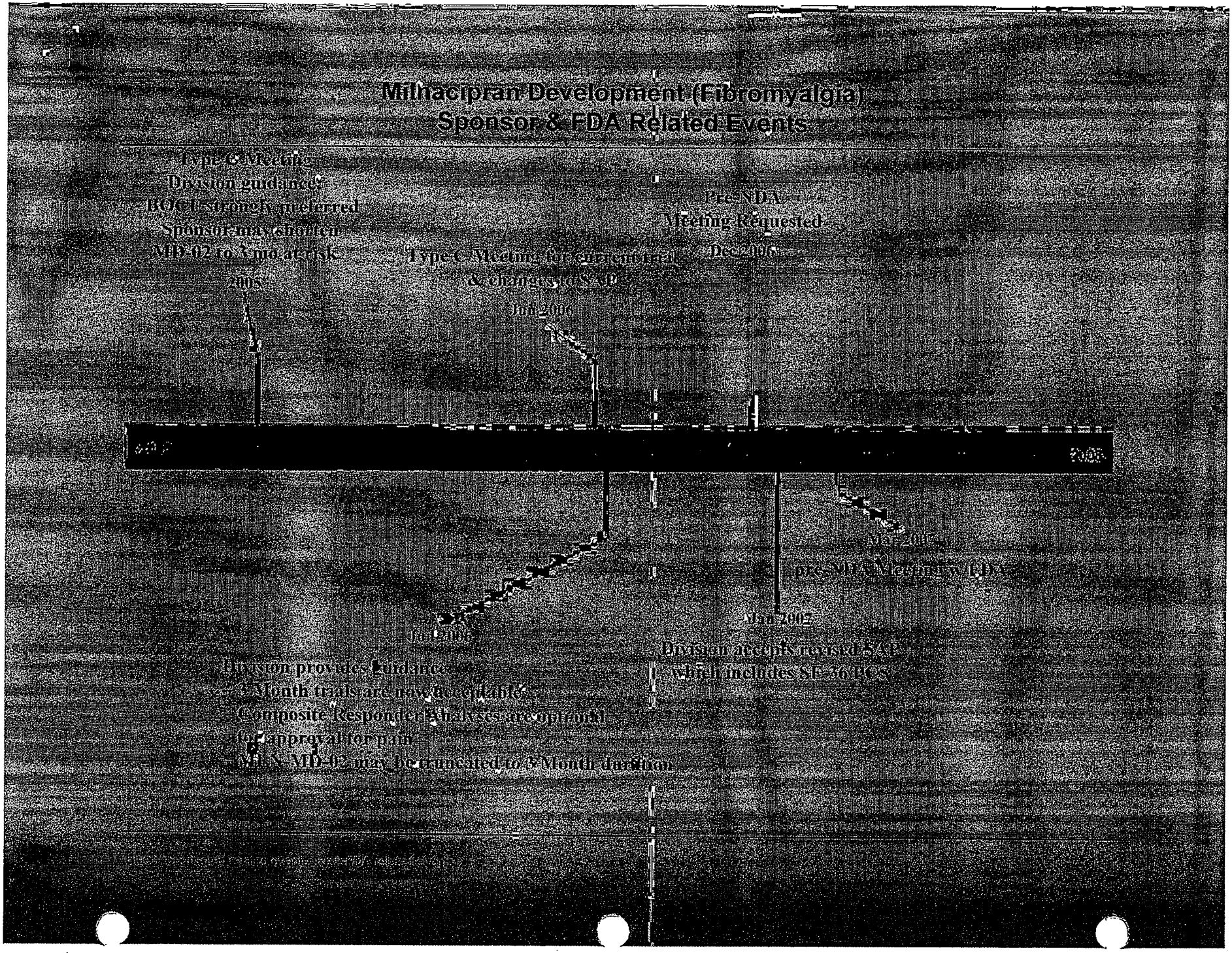

	SPA 2003	Pre-NDA 2007
[redacted]		
Treatment claim	• Pain of FMS based on success on 2-component responder analysis • Fibromyalgia Syndrome based on 3-component analysis	Same
[redacted]		
Definition of responder	• 30% improvement from baseline on VAS using e-diary • Improvement defined as score of 1, 2 or 3 on PGIC • 30% improvement from baseline on the FIQ-PF	• same • Improvement defined as score of 1 or 2 on PGIC • Improvement of at least 6 points on PCS of SF-36

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, M.D. 20857

ATTACHMENT: Mock Adverse Event Data Set

Please note that the HLGT and HLT level terms in this table are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data that is typically found in an adverse event data set.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

ATTACHMENT 2: *Corrected* Mock Adverse Event Data Set

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lowest Level Term (MedDRA Code)	Lowest Level Term (LLT)	Preferred Term (PT)	High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site erythema	Appl site and instillation site reaction	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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/s/

Lauren Tornetta
4/13/2007 10:00:31 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 63,736

Forest Laboratories
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, Pharm.D.
Director, Regulatory Affairs

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Milnacipran (Milnacipran Hydrochloride), for fibromyalgia syndrome.

We also refer to the meeting between representatives of your firm and the FDA on March 16, 2007. The purpose of the meeting was to discuss NDA filing for the fibromyalgia program for Milnacipran Hydrocholride.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2264.

Sincerely,

{See appended electronic signature page}

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

[redacted]

MEMORANDUM OF MEETING MINUTES

MEETING DATE: April 8, 2003

TIME: 10:30 am – 12:00 pm

LOCATION: Corporate S300

APPLICATION (DRUG): IND 63,736 (milnacipran)

SPONSOR: Cypress Bioscience

TYPE OF MEETING: End of Phase 2 Type B Meeting

MEETING CHAIR: James Witter, MD, PhD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Lee S. Simon, MD	Division Director	ODEV/DAAODP, HFD-550
2. James Witter, MD, PhD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
3. Asoke Mukherjee, PhD	Pharmacology Reviewer	ODEV/DAAODP, HFD-550
4. Larry Goldkind, MD	Deputy Director	ODEV/DAAODP, HFD-550
5. Carmen DeBellas, RPh	Chief Project Manager	ODEV/DAAODP, HFD-550
6. Jonca Bull, MD	Director	ODE V
7. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
8. Michael Yao, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
9. Dennis Bashaw, PharmD	Biopharm Team Leader	OPS/OCPB/DPE3/HFD-880
10. Lourdes Villalba, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
11. Sue Ching Lin, MS, RPh	Chemistry Reviewer	OPS/ONDS/HFD-830
12. Josie Yang, PhD	Pharmacology Team Leader	ODEV/DAAODP, HFD-550
13. Joel Schiffenbauer, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
14. Stan Lin, PhD	Statistical Team Leader	OPS/OCPB
15. Terri Rumble, RN	ADRA	ODE V
16. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. [redacted]	Chairman	[redacted]
2. Jay Kranzler, MD, PhD	Chief executive Officer	Cypress Bioscience
3. R. Michael Gendreau, MD, PhD	Chief Medical Officer	Cypress Bioscience
4 [redacted]	Statistical Consultant	[redacted]
5 [redacted]	Electronic Diary Expert	[redacted]
6. Jean-Louis Abitbol	Consultant	Institut de Recherche Pierre Fabre
7. [redacted]	Regulatory Advisor	[redacted]

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PURPOSE OF THE MEETING: To obtain guidance from the Division before proceeding in clinical studies on the use of milnacipran for treatment of the signs and symptoms of fibromyalgia.

PREMEETING COMMENTS:

The Division believes that it is premature to consider this an EOP-2 meeting, rather this should be considered as a general Guidance meeting since there are several issues that need to be addressed further before embarking on phase 3 studies. With this in mind, the Division has the following responses to the Sponsor's questions.

QUESTIONS:

1.1.1. Primary Endpoint Data Collection.

Cypress employed an electronic diary system in the Phase II trial to frequently sample a patient's current and recent pain experience. This diary utilized random prompting methodology for real-time pain assessment, a daily morning report for a daily recall pain assessment, and a weekly report methodology to obtain weekly retrospective pain assessments. The diary also implemented the Gracely Anchored Logarithmic Scale for recording pain symptomatology. Cypress believes that, based on prior work with this diary system by [redacted] and others, as well as the data submitted in the supporting materials for this meeting, that there is adequate evidence to support the utility and validity of this diary system for the collection of a chronic pain endpoint in a pivotal trial. The electronic dairy technology is discussed starting on Page 28 in Section 4.6. The Gracely scale and its characteristics are discussed on Page 25 in Section 4.5. b(4)

a. Cypress wishes to confirm that the Division agrees that the diary system is a valid tool for collecting chronic pain endpoint data in a pivotal trial. b. Additionally, we wish to confirm that the Agency agrees that the Gracely scale is acceptable for use as the measurement scale for the pivotal pain endpoint.

FDA Response:

a. The Division is interested in the use of electronic diaries and understands the potential advantages of this method of data collection. However, there are unresolved issues surrounding this new approach. The Division suggests that the Sponsor submit a review of the literature on the validation of electronic diaries and a full description of the data management, storage and audit path plans. The Division of Scientific Investigations (DSI) will be consulted for input and included in further discussion. All attempts to expedite this discussion will be taken.

b. The Gracely scale, while acceptable as a research tool and acceptable as a component of a clinical trial, is not acceptable for use as the measurement scale for the pivotal pain endpoint for regulatory approval. In fact, there are no regulatory precedents for the use of this scale in clinical analgesic trials. The Division, therefore, prefers that validated pain scales (e.g. VAS, NRS, VRS) be utilized in the pivotal trials.

1.1.2. Composite Primary Endpoint.

The sponsor demonstrated in the Phase II trial that the patient global impression of change at endpoint (PGIC) was highly effective at detecting differences between treated and placebo patients. There is regulatory precedent for use of a PGIC endpoint as a primary outcome measure in this spectrum of pain syndromes (irritable bowel syndrome, tegaserod, July 2002). Based on input from our scientific and medical advisors, Cypress is proposing a composite endpoint as the primary endpoint for our pivotal Phase III trials. The composite endpoint would be a binary, by-patient analysis, modeled after the ACR definition of improvement in rheumatoid arthritis. The composite would require that a patient 1) rate themselves as improved on the PGIC on an intent to treat (ITT)/ last observation carried forward (LOCF) basis at endpoint, AND 2) the patient achieves a clinically meaningful improvement in global pain over baseline, as measured with the electronic diary on a daily basis (4.0 Gracely Units, or approximately 50%). We believe this composite, recommended by our advisory group, satisfies both the desire to have clinically relevant, global outcome measures and the desire for frequent monitoring of key symptom(s) such as pain. Cypress'

proposed composite primary endpoint is discussed in Section 6.3 starting on Page 83.

Does the Division agree that the proposed composite endpoint is acceptable and appropriate, and that the clinical trial design can support approval of the milnacipran NDA?

FDA Response: *No. The Division certainly understands the advantages of a responder index and analysis and encourages development of new indices. However, the Gracely scale, as discussed above is not acceptable as a pain metric and the proposed composite lacks a functional endpoint. At the present time, the Division requires that trials for fibromyalgia succeed in the three co-primary endpoints of pain, function and a patient global assessment.*

The Division invites the Sponsor to explain its discomfort with the Fibromyalgia Impact Questionnaire (FIQ) instrument as a measurement of function for regulatory purposes and to propose alternative instruments.

1.1.3. Treatment Duration.

Cypress believes that a twelve-week, double-blinded drug treatment period is adequate to demonstrate clinically significant improvement in this patient population, and that this time interval is consistent with precedence in rheumatoid arthritis, depression and other chronic conditions where symptomatology is treated in a similar fashion.

Does the Division agree that twelve weeks of double-blinded treatment is sufficient time to demonstrate product efficacy?

FDA Response: *At present, the Division feels that 12-week trials would probably be the minimum acceptable duration for a pivotal clinical trial in fibromyalgia with a drug substance that is well known and understood. However, a 24-week study seems more appropriate for evaluation of a chronic disease with a previously untested drug substance, as is indicated in the Rheumatoid Arthritis (RA) guidance document.*

1.1.4. Concurrent Headache Medications.

During the conduct of the Phase II clinical trial, it became evident that many patients with fibromyalgia also have a high concomitant incidence of migraine headaches. Many patients were concerned about participation in a randomized clinical trial that would prohibit use of appropriately designated migraine medications such as the 5-HT1d agonist class of drugs (triptans). Cypress recently reviewed this issue with the safety personnel at Pierre Fabre, and they concur that there is no apparent medical safety reason for this exclusion.

Does the Division agree that it is acceptable to permit specific migraine medications such as sumatriptan/ rizatriptan for patients experiencing migraine attacks during the conduct of the clinical trial?

FDA Response: *Yes. As long as it is a single chosen therapy and it is recorded and analyzed.*

1.1.5. Sleep Medications.

During the conduct of the Phase II clinical trial, sleep disruption and inability to initiate sleep was a considerable issue. As insomnia is a common problem in fibromyalgia patients, the prohibitions on sleep medications were problematic. Evidence from the Phase II trial indicates that while milnacipran may be beneficial for some patients with respect to their sleep, in general patients do not find milnacipran to be sedating. In this case, other therapies may still be required for FMS patients who have difficulty initiating sleep. Based on the recommendations of our advisors after reviewing this issue, Cypress is requesting the Division's comments on allowing any or all of the following concomitant sleep medications in all Phase III trials:

- trazodone at doses not to exceed 50 mg (i.e. no anti-depressant activity)
- zolpidem/ zaleplon
- diphenhydramine
- chloral hydrate

FDA Response: *Although not the primary endpoint, sleep disturbance is a cardinal symptom in fibromyalgia. The Division recommends that if sleep medications are used, only one drug be allowed and that patients be stratified according to its use. Furthermore, the Division is not clear that trazodone has no effect on depression at the dose suggested.*

It is the Division's understanding that there are no regulatory precedents for the use of the Jenkins Sleep score to evaluate sleep parameters. Please provide the rationale for using this instrument in the fibromyalgia pivotal studies.

1.1.6. Washout Requirements.

Two Phase III trials are proposed in this document. One is a mono-therapy trial similar in design to the Phase II trial previously conducted. The second trial is proposed as a standard of care (SOC) trial where milnacipran will be administered along with a number of currently used treatments for fibromyalgia. The rationale for the second trial design is that partial or incomplete responders to current therapy would have milnacipran added to their current treatment regimen, which would be held constant (similar to how this and other medications are used in clinical practice).

- For the mono-therapy trial, the sponsor intends to allow NSAID usage for pain, as well as anti-histamines and non-benzodiazepine drugs to assist with sleep (Question #5). The Phase II trial prohibition on antipsychotics, antidepressants, and centrally acting pain medications will be maintained. Washout schedules for both trials are listed in the protocol synopses included in the body of the briefing document. See Section 6.2.4, for a listing of excluded medications and the washout interval required.
- For the SOC trial, the only completely prohibited FMS specific medications would be SSRI's or SNRI's, where there may be potential safety issues when combining milnacipran with these compounds due to the potential for excessive serotonergic activity. Low doses of tricyclics, limited to 50 mg amitryptline per day (or equivalent) would be allowed, provided that only low, nighttime doses are used for sleep assistance, and that no changes in dose are initiated during the double-blinded phase of the trial.
- In both studies, any allowed baseline medications would be maintained at stable doses throughout the double-blind treatment phase. Cypress believes that the excellent safety profile that milnacipran has demonstrated, both in the Phase II trial as well as in commercial distribution, minimizes concerns related to adverse events with concomitant therapy. As a result, we have proposed the SOC trial to provide insights as to how physicians might use milnacipran upon commercial availability.

Does the Division agree with our strategy and washout requirements for these two trials?

FDA Response: *For approval, there needs to be replicate evidence of efficacy and safety at the doses proposed in the label. While such trials do not need to be exactly the same design, they need to provide sufficient evidence to answer the regulatory questions for approval. The Division reminds the Sponsor that there needs to be evidence to support the conclusion that the effect size is clinically meaningful. There is concern that the effect of milnacipran in the "SOC" study may not be as great*

as suggested in the monotherapy trial.

1.1.7. Dose Selection and Low Dose Studies.

The second Phase III trial incorporates several arms to evaluate the safety and efficacy of different doses of milnacipran. Based on the results observed with 200 mg in Phase II, we have elected to evaluate two lower doses of milnacipran (25 mg and 100 mg daily), as well as 200 mg, in the SOC trial. The sponsor expects that demonstration of any type of dose response curve in the pivotal trial program will be difficult, as re-uptake inhibitors as a class have typically exhibited very flat dose-response curves. As it is currently written, the trial includes a 25 mg/ day arm; however, the sponsor is interested in eliminating this arm from the trial.

Does the Division require that a low, potentially ineffective dose (25 mg daily) be evaluated as part of the pivotal program? Would it be acceptable to eliminate the 25 mg arm and just incorporate 100 mg, 200 mg and placebo in the second pivotal trial? Does the division have any other comments about dose selection in these two proposed trials?

FDA Response: *The dose-response of milnacipran in fibromyalgia in terms of efficacy or safety has not been adequately established.to date. The Phase 2 program has thus far employed a titration design throughout the entire study with doses of milnacipran that ranged from 50 to 200 mg/day (either as QD or BID dosing) making interpretation of the data very difficult. The Sponsor needs to demonstrate the efficacy and safety of a minimum and maximum dose to be subsequently proposed in the label. Titration is acceptable only during the initial phase of the trial as patients achieve their randomized fixed dose (e.g. placebo or milnacipran). However, patients need to remain on their assigned dose for 12-24 weeks as discussed above. Those patients who do not tolerate upward titration should be discontinued and counted as withdrawals due to an adverse event.*

It is important to identify the lowest efficacious dose. Based on extrapolations from the use of milnacipran as an antidepressant, the Sponsor estimates that the 50-mg/day dose would not be effective in fibromyalgia. However, when used for fibromyalgia, antidepressants are usually prescribed at lower doses than when used for depression. Perhaps the Sponsor could consider a dose-ranging study and another trial using a 50-mg/day dose as a fixed dose during the efficacy assessment period.

Meeting note: *FDA asked the Sponsor to clarify why there is need for upward titration and for tapering before discontinuation (as per the marketed product label); the latter suggests there is a possibility of physical dependence, withdrawal or abuse. The Sponsor stated that the need for upward titration mainly relates to nausea. Furthermore, the Sponsor noted that despite the European labeling recommendation, trials in the US have used no tapering at the end of treatment and showed no evidence of physical dependence or potential for abuse.*

1.1.8. Open Label Continuation.

Both of the proposed trials feature a three month open label continuation phase in which all patients completing the randomized, double-blinded phase of the program would be eligible to continue for an additional three months. The open label continuation phases would use a specified fixed dose that could potentially be different from the double-blinded dose the patient received.

Does the Division have any comments concerning criteria for enrollment in open label continuation or the duration of the open label phase? Does the Division have any comments on whether to allow patients from the Phase II trial to enter the open label continuation phase directly, without going through the double blind Phase III trial first (as they are not eligible for the Phase III due to their prior exposure to milnacipran)?

FDA Response: *While it is acceptable to enroll patients from the phase II or III studies into an open-label study, it is important to design the study in such a way to evaluate patient compliance as well as efficacy and safety in a robust and meaningful way.*

Post Meeting Note: *It is important to note that the Division strongly advises against open-label and uncontrolled extension studies since they are unlikely to provide interpretable information regarding either safety or efficacy.*

1.2. Safety Related Questions

1.2.1. Patient Exposure.

The current Phase III program design will result in approximately 400-600 FMS patients treated in double-blind controlled trials with milnacipran, depending on the results of the interim analyses. These data will supplement the safety data available from the European and Asian safety experience, during which time approximately 2 million patients have used milnacipran at doses ranging from 50 to 200 mg daily. The safety analysis from the Phase II trial is in Section 5.2 starting on Page 60.

Cypress wishes to confirm that, in consideration of the extensive clinical trial and foreign marketing experience with milnacipran, and the resulting widespread worldwide patient exposure, NDA approval would be possible with these planned patient exposure numbers.

FDA Response: *For NDA submission, the Division will require at least minimum ICH guidelines exposure (300 patients exposed for 6 months, 100 for one year at the highest recommended dose) as well as analysis of available post-marketing data.*

1.2.2. Patients Meeting Major Depression Criteria.

Both of the proposed trials exclude patients who meet MINI criteria for "major depressive episode (MDE), current". The Phase II trial enrolled these patients after a careful assessment of suicide risk, and the 3:1 randomization ratio of the Phase II trial minimized the number of patients who were washed off anti-depressants and then assigned to placebo. Based on population studies and the Phase II experience (20 of 125 enrolled patients met MDE criteria), we expect that 15-20% of FMS patients who otherwise would qualify for admission to these trials will meet MDE criteria. Our psychiatric advisors have emphasized that excluding MDE patients is not tantamount to excluding patients with depressed affect or a history of depression, and have recommended that we not enroll these patients during their acute depressive phase. There is also a level of concern about the prospect of enrolling patients currently meeting MDE criteria in a trial where they are potentially removed from antidepressant therapy, and are not under the care of health care professionals experienced in the management of categorical depressed and potentially suicidal patients.

Does the Division have any comments concerning the exclusion of patients who meet criteria for major depression based on the MINI at baseline? Specifically the Sponsor wishes to understand the potential impact of such an exclusion on labeling. Patients with depressed affect, with a past history of depression, who have recovered from an MDE episode, and those who are dysthymic would still be eligible for enrollment under this proposal.

FDA Response: *It is acceptable to exclude these patients but it will be reflected in the label.*

1.3. Statistical Related Question

1.3.1. Interim Analysis.

Both of the proposed trials include a provision to conduct interim analyses based on the triangle method of Whitehead. These analyses would be conducted by an independent DSMB committee, at the point when 50% and 75% of the target enrollment is available for analysis (mono-therapy trial). There is ample precedence for this approach, including a previous pivotal trial program conducted by the sponsor. The primary rationale for interim analysis is to minimize the number of placebo-treated patients if, in fact, a trial has met its efficacy objectives. An independent DSMB would also have the ability to stop the trial(s) for safety reasons, as well as have the ability to request additional, unscheduled analyses at its discretion. The triangle method itself, and specifics of the power calculations for the Phase III trials is contained in Appendix F.

Does the Division have any comments concerning this aspect of the statistical analysis plan?

FDA Response: *The Division discourages the use of interim analyses. Please provide the rationale for such an analysis.*

1.4. CMC and Preclincial Related Question

1.4.1. CMC and Preclinical Issues.

During the initial IND review, the Agency asked several questions regarding the preclinical testing performed in the 1980s and 1990s, and responses to these questions were recently submitted as IND correspondence, serial 004. Likewise, a few comments regarding the closure system mentioned in the IND, as well as a comment regarding use of a positive identity test, were offered by the Agency. These comments have been addressed in IND correspondence, serial 001 and the CMC section of the briefing document.

Does the Division have any additional comments concerning the CMC plans or preclinical testing that has been conducted previously?
In addition to the issues raised above, we trust that the Division will provide further guidance on any other issues that it believes should be taken into account and addressed in preparation for NDA submission.

FDA Response:

1. *It appears that the stability protocol submitted in Appendix G of the briefing package is for the drug product used in clinical trials. The sponsor may submit for review a proposed stability protocol for the primary stability batches of the drug product to support the upcoming NDA. The stability study should be conducted for the drug product packaged in the container closure system proposed for marketing.*

2. *The following comments pertain to the drug product specification:*

   (a) *The dissolution method, including dissolution medium, apparatus, agitation speed, etc., should be finalized prior to the initiation of the primary stability study.*

   (b) *The acceptance criteria of NMT [redacted] % for degradant [redacted] should be qualified if the proposed daily dose is over 100 mg of the drug substance. Refer to Attachment I of ICH Q3B, Impurities in New Drug Products.* b(4)

   (c) *The following two comments conveyed to you on 12/20/01 are repeated here:*

   Content Uniformity should be performed. Identification tests should be specific for the drug substance. Identification solely by the retention time of the major peaks in the HPLC chromatogram is not adequate. If the ID test is not specific, two identification tests using different separation principles are required for the drug product specification. Please refer to ICH Q6A, Section 3.2.2(b).

3. *Please provide an amendment to the IND to update the CMC information, including as appropriate, any changes made in response to the comments above.*

Biopharm Comments:

At the present time, there does not seem to be a bioavailability issue. Because the drug is 90% eliminated by a renal mechanism, the Sponsor will need to evaluate the effect of renal insufficiency on this drug. The Division would also like more details on the studies they have done so that a better assessment of their current program can be done before an NDA is submitted.

Pharm/Tox Comments:

It is recommended that the Sponsor submit full (GLP/QA) non-clinical study reports prior to Phase 3 clinical trials. The Division will provide any necessary recommendations after reviewing data upon receiving submission.

POST MEETING COMMENTS:

The Division is interested in further discussion of the role of paper versus electronic diary data for trial endpoints (i.e. landmark versus time-weighted-average endpoints).

Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence: James Witter, MD, PhD

Drafted by: JADean
Revised by: MLVillalba
JWitter
Initialed by: JWitter
Final: 5/1/03

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/s/

Lee Simon
5/5/03 07:29:44 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	October 14, 2003
TIME:	12 noon
LOCATION:	S300 Corporate Boulevard
APPLICATION (DRUG):	**IND 63,736 (milnacipran)**
SPONSOR:	Cypress Bioscience, Inc.
TYPE OF MEETING:	Type A Meeting, Post Special Protocol Assessment Review
MEETING CHAIR:	James Witter, MD, PhD
MEETING RECORDER:	Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Lee S. Simon, MD	Division Director	ODEV/DAAODP, HFD-550
2. James Witter, M.D., PhD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
3. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
4. Carolyn L. Yancey, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
5. Carmen DeBellas, RPh	Chief Project Manager	ODEV/DAAODP, HFD-550
6. Stan Lin, PhD	Statistical Team Leader	ODEV/DAAODP, HFD-550
7. Paul Z. Balcer	Project Manager	ODEV/DAAODP, HFD-550
8. Lourdes Villalba, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
9. Michael Yao, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
10. Joel Schiffenbauer, MD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
11. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. [redacted]	Cypress Lead Consultant	[redacted]
2. R. Michael Gendreau, MD, PI	Chief Medical Officer	Cypress Bioscience, Inc.
3. Jay Kranzler, MD, PhD	Chief Executive Officer	Cypress Bioscience, Inc.
4. [redacted]	Statistical Consultant	[redacted]
5. [redacted]	Regulatory Advisor	[redacted]

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PURPOSE OF THE MEETING: Type A Meeting for clarification of the Division responses to the Special Protocol Assessment, SN-010.

MEETING OBJECTIVES:

1. To obtain FDA concurrence on protocol modifications.
2. To reach agreement on trial initiation schedule.

QUESTIONS:

1.1 Does the Division agree that the Sponsor's protocol modifications are consistent with the Division's recommendations from the Special Protocol Assessment?

FDA Response: *The Division reminds the Sponsor that the following issues should be clarified in the revised protocol and that the detailed statistical analysis plan (SAP) and trial design of any open-label extensions should be included in the revised protocol:*

1. *The SAP needs to be clear regarding how the indication (i.e. treatment for fibromyalgia syndrome vs. treatment for pain related with fibromyalgia syndrome) will be approached.*

2. *For the functional assessment, Division views the Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) as the primary outcome variable and the SF-36 Physical Component Score (SF-36 PCS) as a secondary outcome variable, which should not worsen during the trial.*

3. *Patients on oral steroids started less than 30 days before the trial should be excluded from any study.*

4. *Patients receiving (or started within 30 days) transcutaneous electrical nerve stimulation, biofeedback, and trigger/tender point injections should be excluded from any study.*

1.2 Does the Division agree that the Sponsor may begin phase III clinical trials while details of data analysis plan and open label extension studies are being finalized with the Division?

FDA Response: *Yes, the Sponsor may begin primary initiation for the milnacipran phase III study program such as selection of study site and recruitment of subjects.*

1.3 Does the division agree that a detailed statistical analysis plan can be finalized in the first quarter of 2004 without prejudice to the phase III program that will begin in October 2003?

FDA Response: *It is acceptable to submit a detailed statistical analysis plan to the Division as proposed in the timeline above and provided data have not been unblinded. The Division prefers that the SAP be completed as early as possible, for example, before significant number of patient recruitment occurs to allow for adequate time to clarify any issues.*

2.1.1 The Sponsor would like to clarify the comments regarding time-weighted analysis at Type A meeting.

FDA Response: *For the time-weighted-average approach, the Division recommends that patients be evaluated at 6-week intervals. The pain and functional outcome needs to demonstrate efficacy on both a landmark (end-of-study) time point as well as a time-weighted average endpoint during the entire trial. The requirement for a minimum of 30% improvement compared with baseline values applies to both outcomes and both time points. The PGA should be a dichotomous yes or no-type outcome.*

2.1.2 The Sponsor would like to clarify the Division 's comments with respect to the patient global variable.

FDA Response: *The currently proposed patient global assessment of change during the trial is similar to that used in the ACR20 criteria for RA and is acceptable as a secondary assessment. The patient global for primary assessment should evaluate the patient's assessment of the therapy.*

2.2 The sponsor would like the Division's feedback on how to deal with the situation where the FIQ-PF is at or near zero at baseline, and therefore no potential exists for any demonstration of improvement.

FDA Response: *The Division views the Fibromyalgia Impact Questionnaire-Physical Function (FIQ-PF) as the primary outcome variable. The Division realizes the potential for both floor and ceiling effect with this instrument. The Division suggests that the SF-36 Physical Component Score (SF-36 PCS) can be employed as a secondary outcome variable during the trial which will be factored in to the overall evaluation of the efficacy results of the trials submitted toward NDA approval. However, it may turn out that the FIQ-PF instrument will not be a useful functional outcome measure.*

2.3.1 The Sponsor wishes to verify that its interpretation of the Division's comments regarding duration of trials is correct, i.e. it is acceptable that FMS32 will be 15 weeks total, and doses of milnacipran other than 100mg and 200mg do not need to be specifically replicated in a 6 months trial.

FDA Response: *Both minimum and maximum effective doses (i.e. any dose proposed for the label) need to be replicated in both the 3 months (or longer) and 6 months (or longer) studies. The analyses planned for the 3-month study should also be performed for the 6-month study, at the 3-month time point, in addition to any planned analyses for the 6-month study.*

2.3.2 The Sponsor wishes to confirm that the FDA agrees that a third pivotal trial (or additional arms in existing trials) is required to meet this requirement.

FDA Response: *To achieve replication of doses, the Division prefers an additional trial rather than adding a study arm in existing trails.*

2.4 Inclusion/Exclusion Criteria

FDA Response: *The Division reminds the Sponsor that inclusion/exclusion criteria may factor into consideration for the final label, assuming adequate evidence of safety and efficacy has been demonstrated in the NDA application. Please see comments above regarding additional exclusions. The "somatic" and "treatment-related" criteria still appear to be too restrictive for this proposed indication.*

2.5 Rescue Medication

FDA Response: *The Division notes that the Sponsor will develop an analysis plan to address the impact of rescue medication usage during the trial. It is important that the use of rescue medications, and how this use will factor in to whether or not a patient is censored from any efficacy analysis plan, be clearly delineated in the SAP.*

2.6 The sponsor seeks clarification of the Division's open label requirements.

FDA Response: *The Division thinks that the proposed open-label extension trial design in SPA (N-009) is not adequate. Ideally, extension studies should be blinded (if possible) with at least one controlling arm to obtain meaningful safety data on a long-term basis. The Division also recommends that there be an efficacy evaluation to address the important issue of durability of treatment response. Enrolling new patients not previously entered in a randomized double-blind, controlled clinical trial should be avoided.*

Minutes Preparer:	Jane A. Dean, RN, MSN
Chair Concurrence:	James Witter, MD, PhD
Drafted by:	JADean
Initialed by:	JWitter
Final:	10/17/03

9/17/08

EXEC CAC MINUTES

Executive CAC
Date of Meeting: Virtual Meeting Sept 9, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Member
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Dan Mellon, Ph.D., PharmTox Supervisor, DAARP
Asoke Mukherjee, Ph.D., Presenting Reviewer, DAARP

Author of Minutes: Dan Mellon, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

IND/NDA # IND 63,736 / NDA 22-256
Drug Name: Milnacipran hydrochloride
Sponsor: Cypress Bioscience, Inc.

Rat Carcinogenicity Study

The review division requested ExecCAC input on the following re-evaluation of thyroid findings in a rat carcinogenicity study. The ExecCAC previously reviewed the findings of a 2-year rat bioassay for milnacipran in 2004 and found the study acceptable; however, the Sponsor was requested to provide a complete examination of the low dose and mid dose histopathology slides of the thyroid for male rats in order to complete the statistical analysis of that tissue. There was no suggestion of increased thyroid C-cell tumors in female rats. The results and revised incidences are summarized in the table below:

Incidence of Thyroid C-Cell Tumors: Male Rats

	Control I and II	**5 mg/kg**	**15 mg/kg**	**50 mg/kg**	**Dose Response p-values**	**Pairwise p-values**
No. Examined	99	53	47	51		
Adenoma	5 5%	6 11%	6 13%	11* 21.5%	0.0020	0.0026
Carcinoma	1 1%	1 2%	0	0	0.6800	1.0000
Adenoma + Carcinoma	6 6%	6 11%	6 13%	11* 21.5%	0.0035	0.0057

* Statistically significant compared to combined control group via pairwise comparison.

The sponsor concluded that although statistically significant for both trend analysis and pairwise tests and occurring at an incidence greater than the concurrent controls, the

incidence is still within the historical control range fo: —— (data from the 8 most recent carcinogenicity studies at the time of the written study report ranged from 4-24%, see below). The Sponsor also noted that the male control groups in this study showed an unusually low incidence of C-cell tumors for that laboratory. The Sponsor's summary table for historical data on thyroid C-cell adenomas from the conducting laboratory compared to controls is reproduced below:

b(4)

Text table 1. Background tumour incidence data of thyroid C-cell adenomas compared with control and high dose groups in this study

Study#	C-cell adenoma Percentage incidence M	F	Termination date Month/Year
A	24	12	11/88
B	20	11	9/88
C	17	15	6/88
D	16	2	2/88
E	18	16	1/88
F	12	8	6/87
G	17	14	6/87
H	11	10	4/87
314/58 group 1	8	22	3/89
314/58 group 4	22	8	
314/58 group 5	4	20	

not all studies have been subjected to quality assurance audit at the time of writing this report

Executive CAC Recommendations and Conclusions:

The Executive CAC concluded that the increase in the incidence of thyroid C-cell adenoma and combined adenomas and carcinomas in male rats treated with 50 mg/kg milnacipran were treatment-related and that this finding should be included in the drug product labeling.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DAARP
/Dan Mellon, DAARP
/Asoke Mukherjee, DAARP
/Beth Bolan, DAARP
/Diana Walker, DAARP
/ASeifried, OND IO

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/s/

R. Daniel Mellon
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PHARMACOLOGIST

David Jacobson-Kram
9/17/2008 07:59:52 AM
PHARMACOLOGIST

7/3/08

Executive CAC
Date of Meeting: July 1, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Anne Pilaro, Ph.D., DBOP, Alternate Member
R. Daniel Mellon, Ph.D., DAARP, Team Leader
Elizabeth Bolan, Ph.D., DAARP, Presenting Reviewer

Author of Minutes: Elizabeth Bolan, Ph.D., DAARP

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-256
Drug Name: Milnacipran Hydrochloride
Sponsor: Forest Laboratories, Inc.

Background:

Milnacipran hydrochloride is a non-tricyclic antidepressant which inhibits the reuptake of norepinephrine and serotonin. It is approved for the treatment of depression in several countries at a maximum dose of 50 mg BID. The indication sought for this NDA is treatment of fibromyalgia syndrome with a maximum dose of 100 mg BID.

A 26-week Tg.rasH2 mouse carcinogenicity study was submitted as part of the NDA submission. The formal review of the carcinogenicity study can be found in the NDA review. The basis for dose selection for the 26-week Tg.rasH2 study was MTD from a 28-day dose range finding study. The high dose of milnacipran used in the 26-week study was 125 mg/kg. This dose was recommended by the eCAC (October 18, 2005) on the basis of its being half of the lethal dose (250 mg/kg) observed in the 28-day dose range finding study. The low dose of 25 mg/kg is approximately equal to a human daily dose of 200 mg, which is the highest dose proposed to be marketed in the NDA.

Milnacipran was found to be negative in the Ames Test, *in vitro* chromosomal aberration assay in purified human lymphocytes, L5178Y TK +/- mouse lymphoma forward mutation assay, and in the *in vivo* mouse micronucleus assay.

Tg.rasH2 Mouse Carcinogenicity Study

The doses (25, 50 and 125 mg/kg) used in this study and the use of urethane as a positive control were recommended by the eCAC. The vehicle used was sterile water.

Daily treatment with milnacipran HCl up to 125 mg/kg did not result in an increase of neoplastic lesions. The most frequent neoplasms noted included pulmonary tumors,

hemangiomas and hemangiosarcomas. A trend test for hemangiosarcomas (multiple organs combined) in females was significant: however, no significant pairwise comparisons were seen. The incidence of hemangiosarcomas observed for females was similar to the historical control values provided by the Sponsor and those previously seen in studies submitted to the FDA. Various neoplasms or pre-neoplastic lesions were observed but all were similar to levels observed in vehicle controls and/or similar to levels observed in the historical controls.

Executive CAC Recommendations and Conclusions:

Tg.rasH2 mouse final study:

- The Committee agreed that the study was adequate, noting prior Executive CAC concurrence with the doses used.

- The Committee agreed that the study was negative for any statistically significant drug-related neoplasms

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
NDA 22-256/Division File, DAARP
R. Daniel Mellon/Supervisor, DAARP
Elizabeth Bolan/Reviewer, DAARP
Diana Walker/CSO/PM, DAARP
Adele Seifried, OND IO

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/s/

David Jacobson-Kram
7/3/2008 08:19:36 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE:	January 8, 2009
TO:	Diana Walker, Regulatory Project Manager Jane Filie, M.D., Medical Officer Division of Anesthesia, Analgesia, and Rheumatology Products
FROM:	Michelle Chuen, M.D. Good Clinical Practice Branch 1 Division of Scientific Investigations
THROUGH:	Constance Lewin, M.D., M.P.H. Branch Chief Good Clinical Practice Branch 1 Division of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspection
NDA:	22-256
APPLICANT:	Cypress Biomedical, Inc.
DRUG:	Milnacipran hydrochloride
NME:	Yes
THERAPEUTIC CLASSIFICATION:	Standard Review
INDICATIONS:	Treatment of fibromyalgia
CONSULTATION REQUEST DATES:	February 28 and October 7, 2008
DIVISION ACTION GOAL DATE:	October 15, 2008
PDUFA DATE:	October 18, 2008

I. BACKGROUND:

On August 28, 2008, the Division of Scientific Investigations, Good Clinical Practice Branch 1, submitted a clinical inspection summary for NDA 22-256 to the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). The clinical inspection summary summarized the findings for inspections of eight clinical investigators and Forest Laboratories, Inc., as a contract research organization (CRO).

On October 7, 2008, DAARP received a complaint regarding data integrity in Protocol #MLN-MD-02. Among other items, the complainant alleged that 57 study participants did not have Personal Electronic Device (PED) data at the three-month primary study endpoint, that the PED data for only the 23 subjects known to be positive responders to milnacipran were recovered, and that data for the 34 subjects not known to be positive responders were not recovered. Per the Review Division, the 23 subjects in question were not "known to be positive responders to milnacipran" but rather were *possible* responders to milnacipran *or placebo,* whereas the other 34 patients were known *not* to be responders regardless of what additional data were recovered. Furthermore, 22 of the 23 subjects were classified as nonresponders even with the retrieved data, and the one classified as a responder was in the placebo group.

The review division, DAARP, requested an inspection to evaluate the complaint allegations and to determine and document the incidence of lost and broken PEDs, PED replacement procedures, and procedures for handling the PED data for patients with lost or broken PEDs. The inspection assignment was issued in October 2008 and the inspection was conducted, at Forest Laboratories, Inc., in early December 2008. This clinical inspection summary addendum is provided to summarize the results of this re-inspection at Forest Laboratories to investigate the complaint.

II. RESULTS:

Name of Contract Research Organization	**Protocol #**	**Inspection Dates**	**Final Classification**
CRO: Forest Laboratories, Inc. Michael K. Olchaskey, PharmD Director, Regulatory Affairs Forest Research Institute Jersey City, New Jersey	FMS 031 and MLN-MD-02	01 Dec-03 Dec 08	NAI

Key to Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

CRO:
Forest Laboratories, Inc.
Michael K. Olchaskey, PharmD
Director, Regulatory Affairs
Forest Research Institute
Jersey City, New Jersey

a. **What was inspected**: The inspection included review of, but was not limited to, the following: organizational responsibilities, monitoring procedures, quality assurance, data collection and handling, automated data entry, and the overall integrity of the efficacy data that was submitted through the patient electronic diaries (PEDs).

b. **General observations/commentary**: In Study FMS031, 8 subjects in the 100 mg milnacipran dose group and 24 subjects in the 200 mg milnacipran dose group had PED malfunctions and were classified as responders. In Study MLN-MD-02, 30 subjects in the 100 mg milnacipran dose group and 26 subjects in the 200 mg milnacipran dose group had PED malfunctions and were classified as responders. These numbers exclude any patients for whom the PED malfunction was able to be resolved at the study site (battery failures, etc.). The sponsor did not have any standard operating procedures in place for replacing malfunctioning PEDs.

   No regulatory violations were noted.

c. **Assessment of data integrity**: If the above numbers of possible misclassifications due to PED malfunctions do not adversely impact the efficacy results, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

We recommend that DAARP evaluate whether the above numbers of possible misclassifications due to PED malfunctions adversely impact the efficacy results. Provided the efficacy results are not adversely impacted, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

(See appended electronic signature page)

Michelle Chuen, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Constance Lewin
1/13/2009 10:32:34 AM
MEDICAL OFFICER
Entered into DFS by branch chief on behalf of primary reviewer Dr. Michelle Chuen.

8/28/08

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE:	August 28, 2008
TO:	Diana Walker, Regulatory Project Manager Jane Filie, M.D., Medical Officer Division of Anesthesia, Analgesia, and Rheumatology Products
FROM:	Roy Blay, Ph.D. Good Clinical Practice Branch 1 Division of Scientific Investigations
THROUGH:	Constance Lewin, M.D., M.P.H. Branch Chief Good Clinical Practice Branch 1 Division of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections.
NDA:	22-256
APPLICANT:	Cypress Biomedical, Inc.
DRUG:	Milnacipran hydrochloride
NME:	Yes
THERAPEUTIC CLASSIFICATION:	Standard Review
INDICATIONS:	Treatment of fibromyalgia
CONSULTATION REQUEST DATE:	February 28, 2008
DIVISION ACTION GOAL DATE:	October 15, 2008
PDUFA DATE:	October 18, 2008

I. BACKGROUND:

Milnacipran hydrochloride is proposed for the treatment of fibromyalgia. Milnacipran is a dual noradrenaline and serotonin re-uptake inhibitor (NSRI) and has been used in the treatment of clinical depression and fibromyalgia. In Protocol FMS 031, subjects are treated with the test article for 27 weeks and record their experiences in an electronic diary.

The primary efficacy parameter is based on subject recollection and recordation of pain experienced. Similarly, for Protocol MLN-MD-02, the primary efficacy endpoint is based on subject recall of pain experienced and recorded following treatment with one of two doses of milnacipran or placebo.

The protocols and sites were selected because both studies were very large with multiple participating centers.

The protocols inspected include:

FMS 031, "A Phase III Pivotal, Multi-center, Double-Blind, Randomized, Placebo-Controlled Mono-therapy Study of Milnacipran for Treatment of Fibromyalgia", and

MLN-MD-02, "A Phase III Pivotal. Multicenter, Double-Blind, Randomized, Placebo-Controlled Monotherapy Study of Milnacipran for Treatment of Fibromyalgia".

A limitation of this inspection at all sites as a result of protocol design was the ability to verify primary endpoint data involving patient pain recall. The subject's recall of pain levels for the previous 24 hours was recorded via electronic diary and directly downloaded from the diary to Invivo Data which in turn provided a CD of this data to the clinical investigator. While this CD of endpoint data could be compared with data listings, such a comparison would not verify that the data submitted by the subject was the same as that submitted by Invivo Data to the investigator. This limitation on data verification was discussed with the reviewing medical officer, Dr. Filie, who in turn indicated that she had discussed the matter with her supervisor. Dr. Filie acknowledged an understanding regarding the limitations on verification of data collected and submitted as described above.

1. Dr. James L. Borders
(previous clinical investigators were
Dr. Sylvia L. Cerel and Dr. John E. Pappas)
Central Kentucky Research
Associates, Inc.
3475 Richmond Road, 3rd Floor
Lexington, KY 40509

   a. **What was inspected**: For protocol FMS 031, signed consent forms were present for all 92 screened subjects. The records of 22 of the 38 subjects completing the study were reviewed in depth. Source documents were compared with the corresponding CRFs and the data listings. Primary endpoint assessment data of Patient Global Impression of Change (PGIC), the Fibromyalgia Impact Questionnaire (FIQ) and the SF-36 were reviewed. Other records reviewed included, but were not limited to, adverse events, concomitant medications, and drug accountability.

   b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

   c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

   Observations noted above are based on review of the preliminary report. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. Dr. Francis X. Burch
Radiant Research San Antonio, NE
8527 Village Drive, Suite 207
San Antonio, TX 78217

   a. **What was inspected**: For protocol FMS 031, 39 subjects were enrolled and the records of ten subjects were reviewed in depth. Source documents were compared with provided data listings with regards to early terminations, protocol deviations, adverse events, concomitant medications, laboratory results, and primary efficacy data.

   b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

   c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

3. Dr. Christopher D. Alftine, M.D.
   Medford Medical Clinic, LLP
   555 Black Oak Drive, Suite 310
   Medford, OR 97504

   a. **What was inspected**: For protocol FMS 031, consent forms for all 54 subjects were reviewed. 33 subjects were randomized to the protocol with 16 subjects completing the study. Primary efficacy parameters of the Fibromyalgia Impact Questionnaire Physical Function Score (FIQ), and Patient Global Impression of Change (PGIC), were verified for all 33 subjects. Subject records for four of the subjects were reviewed in depth, including, but not limited to, case report forms, subject eligibility criteria, ECG and lab reports, and test article accountability.

   b. **General observations/commentary**: Subject 10108 was treated with a codeine-containing medication within the two-week period prior to visit Tx 15, in violation of the protocol. A waiver was not obtained for this treatment, nor was this change in research activity reported to the IRB. Three subjects (#s 10120, 10144, and 10147) were treated with benzodiazepine for anxiety. Though waivers were obtained for this treatment, this change in research activity was not reported to the IRB. Six subjects (#s 10119, 10112, 10144, 10150, 10153, and 10154) did not receive, or did not receive in a timely manner, revised versions of the IRB-approved informed consent documents for their review and signature. These revised consent forms contained additional risk information including, but not limited to, convulsions/seizures, increased heart rate, and symptoms of depression.

   c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

4. Dr. Richard L. Weinstein, M.D.
   Diablo Clinical Research, Inc.
   2255 Ygnacio Valley Road, Suite M
   Walnut Creek, CA 94598

   a. **What was inspected**: For protocol FMS 031, 46 subjects were screened, 31 subjects were randomized, and nine subjects completed the study. All consent forms were reviewed. Subject records for 15 of the subjects were reviewed in depth, including, but not limited to, the Fibromyalgia Impact Questionnaire Physical Function (FIQ-PF) and the Patient Global Impression of Change (PGIC). Additional parameters reviewed included test article accountability, inclusion/exclusion criteria, concomitant medications, screening procedures, washout periods, adverse event reporting, and IRB oversight.

   b. **General observations/commentary**: One subject (# 15343) did not sign the appropriate IRB-approved consent form for participation in study FMS-031. The site maintained inadequate records of drug disposition for several subjects (#s 15318, 15324, 15328, 15331, 15334, 15341, 15343 and 15340) at various study visits.

c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

Observations noted above are based on review of the preliminary report. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

5. Dr. R. David Ferrera, M.D.
Sacramento Research Medical Group
107 Scripps Drive, Suite 210
Sacramento, CA 9582

a. **What was inspected**: 112 subjects were screened, 73 subjects were randomized, and 30 subjects completed the study to treatment #29. All consent forms were reviewed. Study records for 36 subjects were reviewed in depth, including, but not limited to, source documents, case report forms, subject eligibility criteria, ECGs, lab reports, and test article accountability.

b. **General observations/commentary**: One subject (# 296-13) was dispensed the study drug rather than the assigned placebo. One subject (#243-85) had vesicular lesions on the forehead noted in the source records but not recorded on the case report forms.

c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

6. Dr. John Prospero Gresh
Renstar Medical Research
104 SE 1st Avenue, Suite B
Ocala, FL 34471

a. **What was inspected**: 41 subjects were enrolled with 21 completing the study. Signed consent forms were present for all subjects. The patient Global Impression of Change (PGIC), Fibromyalgia Impact Questionnaire (FIQ) and the Physical Component Summary of Short Form 36 (SF-36 PCS) were reviewed. An additional 12 records were reviewed in their entirety. Other records were also reviewed with respect to documentation of adverse events and concomitant/rescue medications.

b. **General observations/commentary**: Two subjects (#s 214-07 and 214-50) took rescue medications in violation of the protocol, subject 214-40 was randomized to the study prior to an evaluation of qualifying laboratory results, some adverse events experienced by subject 214-40 were not reported to the sponsor, and subject 214-22 did not sign the informed consent document.

c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

7. Dr. Mark W. Graves
Welborn Clinic
421 Chestnut Street
Evansville, IN 47713

a. **What was inspected**: 37 subjects were randomized to the study. The records of 19 subjects were reviewed in depth (seven receiving placebo and 12 receiving the test article). Select study records were reviewed for seven subjects who were terminated early in the study and for seven more subjects that were screen failures. Records reviewed included, but were not limited to, ECG tracings, medical histories, psychological evaluations, Physician Global Impression of Change (PGIC) assessments, SF-36 forms, concomitant medications, adverse events, and test article accountability.

b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

8. Dr. Dana R. Trotter
Arthritis Clinic
5439 Durand Avenue, Suite 103
Racine, WI 53406

a. **What was inspected**: 34 subjects were randomized to the study. 14 subjects completed the study. Records for four subjects that completed the study were reviewed including medical records, source documents, drug accountability records and CRFs. In addition the records of two screen failures and five subjects that were randomized but terminated early were also reviewed. Other records reviewed included adverse event reporting, concomitant medications, rescue medication usage, SF-36 and Patient Global Impression of Change (PGIC) assessments.

b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. **Assessment of data integrity**: As discussed above, pain recall data, one of the primary endpoints, could not be verified. Remaining data appear acceptable in support of the respective application.

9. CRO:
   Forest Laboratories, Inc.
   Michael K. Olchaskey, PharmD
   Director, Regulatory Affairs
   Forest Research Institute

   a. **What was inspected**: The inspection included review of, but was not limited to, the following: organizational responsibilities, selection and monitoring of clinical investigators, monitoring procedures, quality assurance, adverse event reporting, data collection and handling, automated data entry, and drug accountability.

   b. **General observations/commentary**: The inspection noted an inadequate drug reconciliation process based on the count of blister packs rather than individual capsules of test article. The return of the test article in partial blister packs and/or kits resulted in discrepancies between the amount of test article dispensed and the amount returned.

   c. **Assessment of data integrity**: The electronic patient-reported outcomes (ePRO) system used by Invivo Data, Inc., to capture data on subject pain recollection was reviewed, including validation reports, 21 CFR Part 11 compliance, and audit trails. Study data stored on Invivo's servers received a cursory review during this sponsor inspection. During the inspections of the clinical sites, it was determined that data directly downloaded from the subject's electronic diary to Invivo Data was in turn provided to investigators as a data CD at the conclusion of the study. While this CD of endpoint data could be compared with data listings, such a comparison would not verify that the data submitted by the subject was the same as that submitted by Invivo Data to the investigator. Otherwise, data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As noted above, the endpoint data involving patient pain recall over the previous 24-hour period (a primary endpoint) was directly downloaded from the subject's electronic diary to Invivo Data which in turn provided a CD of this data to the clinical investigator. While this CD of endpoint data could be compared with data listings, such a comparison would not verify that the data submitted by the subject was the same as that submitted by Invivo Data to the investigator. The review division should consider the impact of the inability to verify this particular dataset on overall data acceptability.

Review of the establishment inspection reports (EIRs) for Drs. Borders and Weinstein are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR(s).

Other than consideration of the issue of data verification discussed above, the data generated by the clinical sites of Drs. Borders, Burch, Alftine, Weinstein, Ferrera, Gresh, Graves, and Trotter, and the sponsor, Forest Laboratories, appear acceptable in support of the respective application.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Roy Blay
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CSO

Constance Lewin
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