MDL_PROD_NO = MDL-FOREM0018197
CD_NAME = MDLDVD005
FROM : Bose, Anjana </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=ANJANA.BOSE>
TO : Fico, Theresa </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=THERESA.FICO>; Gergel, Ivan </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=IVAN.GERGEL>; Shusterman, Neil </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=NEIL.SHUSTERMAN>; Jackson, Robert </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=ROBERT.JACKSON>; Castellana, John </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=JOHN.CASTELLANA>; Macalush, Michael </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=MICHAEL.MACALUSH>; Assenza, Sebastian </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=SEBASTIAN.ASSENZA>; Mahashabde, Shashank </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=SHASHANK.MAHASHABDE>; Dedhiya, Mahendra </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=MAHENDRA.DEDHIYA>; Lindamood, Charles </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=CHARLES.LINDAMOOD>; Gray, William </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=WILLIAM.GRAY>
CC : Schlackman, Eric </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=ERIC.SCHLACKMAN>; Ventura, Daniel </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=DANIEL.VENTURA>; Zheng, Hongjie </O=FOREST LABORATORIES/OU=FRX/CN=RECIPIENTS/CN=HONGJIE.ZHENG>
DATE = 02/25/2007
TIME : 6:13 PM
SUBJECT : RE: DRAFT Lexapro Road Map
SOURCE : Michael Macalush
ATTACHMENT : .\Attachment\MDL-FOREM0018197\001.AB comments_LEX ROAD MAP Jan 07.doc
BODY : From: Bose, Anjana
Sent: Sunday, February 25, 2007 6:13:25 PM
To: Fico, Theresa; Gergel, Ivan; Shusterman, Neil; Jackson, Robert; Castellana, John; Macalush, Michael; Assenza, Sebastian; Mahashabde, Shashank; Dedhiya, Mahendra; Lindamood, Charles; Gray, William
CC: Schlackman, Eric; Ventura, Daniel; Zheng, Hongjie
Subject: RE: DRAFT Lexapro Road Map

Attachments: AB comments_LEX ROAD MAP Jan 07.doc

Terry,

Thank you for preparing the draft. It follows the discussion on Feb 5th and I understand that everything hinges on SCT-32.

But, I am a bit confused about the timing of the briefing book and its contents. As indicated, the SCT-32/32A results are expected end of November. So, there will be no data from the ongoing study in the briefing book planned to be submitted in July and only data that can be provided are from the old citalopram and the MD-15 study which have all been submitted to FDA. Should the August meeting (assuming it is meant to be a pre-sNDA meeting) wait until end of the year?

We definitely have to revive the contact regarding the submission strategy and if it is only the plan, could it be done as a proposal as done previously with other submissions without a briefing book?

Also, as much as I know, we have not heard back from FDA regarding the Forest response to FDA comments on SCT-MD-32 SAP submitted in Jul/Aug 2005. In addition, the 16-week protocol amendment for SCT-32A was submitted recently. It will be helpful to follow-up on these two items prior to submitting the SAPs

Attached is the document with annotated commnets. Please feel free to contact me if there are any questions.

Thanks,
Anjana

———

From: Fico, Theresa
Sent: Fri 2/23/2007 9:17 AM
To: Gergel, Ivan; Shusterman, Neil; Jackson, Robert; Castellana, John; Macalush, Michael; Bose, Anjana; Assenza, Sebastian; Mahashabde, Shashank; Dedhiya, Mahendra; Lindamood, Charles; Gray, William
Cc: Schlackman, Eric
Subject: DRAFT Lexapro Road Map

Dear colleagues

Attached is the draft Lexapro Road map from our meeting of February 5th. Please review and provide comments by EOB Wednesday, February 24, 2007.

Many thanks,

Terry

Theresa Fico, PhD

Senior Director,

Corporate Project Managment

Forest Research Institute

P: 201-427-8043

F: 201-427-8100

Lexapro IR Operational Road Map

Last Updated: 2/05/07
Key Owner(s): A. Bose, B. Gray

1. Background Information

Date Licensed	*Indication(s)*	*Current Phase*	*Date of Next Decision Point*	*Patent*
	Adolescent MDD	III	November 29, 2007	March 2012

This document will focus on the immediate release formulation for major depressive disorder (MDD). Specifically, two ~~-~~trials are on-going, one in acute treatment (SCT-MD-32), and the other a double-blind extension ~~relapse prevention~~ (SCT-MD-32A) in adolescents. The efficacy and safety results from a ~~A~~ previously completed trial (SCT-MD-15) ~~has shown the following results (post-hoc analysis) on efficacy~~are presented in Tables 1 and 2. The trial failed to show significance in primary parameter, change from baseline in CDRS-R at Week 8 (LOCF) but a post-hoc analyses yielded significance in secondary parameters in the adolescent population.

Table 1 Summary of Efficacy Results (LSMD)- ITT Population

Parameter	*Time Point*	*All Patients*		*Adolescents (12-17 years)*	
		Placebo (N=132)	*Escitalopram (N-129)*	*Placebo (N=80)*	*Escitalopram (N=77)*
CDRS-R (Primary)	Baseline	56.6	54.5	57.2	55.4
	Change at Week 8 (LOCF)	-20.2	-21.9	-17.5	-20.1
	Change at Week 8 (OC)	-20.8	-23.9[@]	-17.8	-22.3*
CGI-I[‡] (Secondary)	Week 8 (LOCF)	2.5	2.3	2.8	2.4 *
	Week 8 (OC)	2.4	2.1	2.7	2.2*
CGI-S (Secondary)	Baseline	4.4	4.2	4.4	4.2
	Change at Week 8 (LOCF)	-1.3	-1.6[@]	-1.0	-1.5*
	Change at Week 8 (OC)	-1.4	-1.8*	-1.1	-1.7**
CGAS (Secondary)	Baseline	51.9	52.9	51.5	52.1
	Change at Week 8 (LOCF)	12.7	15.6[@]	10.0	15.7**
	Change at Week 8 (OC)	13.6	16.8*	11.4	17.0**

* $p \leq 0.05$, ** $p < 0.01$, [@] $p < 0.10$; based on ANCOVA model with treatment group, study center, and age group as factors and baseline score as covariate (for CGI-I, baseline CGI-S score was used).
[‡] CGI-I data represent values at Week 8.
LSMD=Least square mean difference; ITT: Intent-to Treat; N= number of patients in ITT Population

Table 2 **Most Frequent Treatment Emergent Adverse Events (≥5% in Either Treatment Group) – Safety Population**

Preferred Term	*Placebo (N=133) n (%)*	*Escitalopram (N=131) n (%)*
Patients With at Least 1 TEAE	90 (67.7)	90 (68.7)
Headache	29 (21.8)	30 (22.9)
Abdominal Pain	7 (5.3)	14 (10.7)
Nausea	6 (4.5)	10 (7.6)
Inflicted Injury	10 (7.5)	9 (6.9)
Rhinitis	8 (6.0)	8 (6.1)
Pharyngitis	8 (6.0)	7 (5.3)
Upper Respiratory Tract Infection	8 (6.0)	7 (5.3)
Vomiting	5 (3.8)	7 (5.3)
Menstrual Cramps*	7 (10.1)	3 (4.4)
Diarrhea	8 (6.0)	5 (3.8)
Influenza-Like Symptoms	8 (6.0)	3 (2.3)

* Percentages are based on the number of female patients (placebo, *N=69*; escitalopram, *N=68*).

Following these results, SCT-MD-32 was planned to evaluate escitalapram in adolescence with an increased sample size.

2. Issues Requiring Resolution (Within the Next Year/Phase of Development)

There are only two items that need resolution and those revolve around 1) establishing definitive efficacy and safety within the adolescent MDD clinical program (SCT-MD-32), and 2) obtaining FDA agreement on the sNDA submission strategy.

3. Timings and Criteria for Next Steps/Decisions

Study/Activity	Status
SCT-MD-32	LPLV 5/31/07, top line 11/29/07
SCT-MD-32A	LPLV 9/25/07 (truncated to 16 week treatment), topline 11/29/07

- FRI recommendation for a **No-Go** would be determined by the efficacy & safety results of SCT-MD-32. The various possibilities are

(1) ~~if SCT-MD-32 fails to demonstrate~~ No statistical significance (p> 0.05) of escitalopram ~~versus placebo~~ on the ~~Children's Depression Rating Scale-Revised (CDRS-R), the~~ primary efficacy variable, CDRS-R using LOCF analyses as well as the two sensitivity analyses (MMRM and OC)~~,~~

or

(2) an unfavorable tolerability profile.

This recommendation is based upon 1) results observed in the post-hoc analysis from SCT-MD-15 and 2) a large sample size per group in the study (150 per group) which is expected to provide at least 80% power assuming an effect size (treatment group difference relative to pooled

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standard deviation) of 0.325.~~provides a xx% power to detect a xx difference between (to be provided by clinical development) escitalopram and placebo.~~

- If the (esc-placaebo) difference is between 0.05 and 0.01 on the primary analyses but significant based on at least one of the two senstivity analyses, or if the pooled analyses using the data from SCT-MD-15 and SCT-MD-32 yields statistical significance, or there is statistical significance on the secondary parameters, then the submission strategy will be revisited.

- **NDA Submission Strategy**: The plan is to use the ~~same approach as in the past to~~ bridging strategy , with one positive study with ~~e between~~ citalpram (CIT-MD-18) and one positive study with escitalopram (. ~~The acute MDD efficacy study (~~SCT-MD-32). The success of SCT-MD-32 is critical ~~must be successful in order~~ to pursue this strategy.
  - All four placebo-controlled acute s~~S~~tudies will be included ~~to be discussed~~ in the ISE. The efficcay claim will be based on the data from CIT-MD-18 ~~and LU 9404 (provide bridging to citalopram data) as well as~~and SCT-MD-32. Additional supportive analyses with subsets of data from ~~A post-hoc analysis of~~ SCT-MD-15 and 94404 will be ~~(including adolescents from 12 – 17 years of age) will be considered supportive and hence~~ included. In addition, if SCT-MD-32A is also positive, the application will also seek the maintenance claim.
  - The ISS will include data from all pediatric studies, ~~be composed of~~ pooled data from SCT-MD-15, SCT-MD-32, and SCT-MD-32A, and citalopram studies (CIT-MD-18, 19, 20, and 94404), along with data from PK studies.
  - Due to the sensitivity of this topic, this submission will more than likely prompt the FDA to bring this in front of an advisory committee.

4. Action Items (what, by whom and by when including communication)

- Submit a proposal to FDA, describing the submission plan to follow-up on the previous communication as well as to clarify if the data from SCT-MD-32A along with the data from the lead-in study (24-week total) is adequate to seek a efficacy maintenance claim.
- **Submit SCT-MD-32/32A SAP to FDA:** So that input from FDA would likely be received prior to submission of Briefing Book (Clinical Team)

[Comment: SCT-32 SAP was submitted in May 2005; FDA commented in July 2005, Forest submitted response. As much as I know we have not received a feedback on the response. So, it is critical that we follow up on this topic prior to submitting the next version. Also, it will be helpful to get some feedback on the SCT-32A amendment submitted, primarily if the primary parameter as defined will give the maintenance indication. This will impact the finalization of SCT-32A SAP]

- **Request Pre-NDA meeting:** A FDA meeting will be requested by May in order to target an August meeting. (Regulatory)
-

[Comment: This briefing book (target completion July) will not have any efficacy data from SCT-32, which is the critical second study for the sNDA submission. It is my experience that a briefing book for a pre-NDA meeting always provides data on the pivotal studies, at least the primary paramaeter to help the Agency provide guidance. It is my understanding that the final clinical study report for SCT-15 have been submitted to FDA; so there is no new data to be included in the briefing book and I am not sure what new information will be included as there is no new data from citalopram.]

- **Pre-NDA Meeting Briefing Book**: A briefing book to discuss the adolescent MDD filing will be completed by July 2007. (Project Team)
- **Pre-NDA Meeting with FDA -** To review the format of the submission and obtain their agreement planned to be ready in August 2007. (Regulatory Department)

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- **Obtain results of SCT-MD-32 and SCT-MD-32A**: top line expected November 29, 2007. (Action: Medical)
- **File sNDA:** If positive, the plan is to file the sNDA by June 2008. (Project Team)