NDA #11-961

52 | ORIG.

STATISTICAL REVIEW AND EVALUATION

NDA#: 11-758/DESI

NOV 20 1987

Applicant: Hoffmann-La Roche Inc,

Name of Drug: Marplan® (isocarboxazid)

Indication: Treatment resistant depression

Documents Reviewed: Volumes 1-4 of the resubmission dated October 22,1987.

The Marplan DESI application was originally reviewed by Mr. Daniel Marticello on August 4, 1982. In his review, Mr. Marticello noted that limiting the analysis to patients that had been treated with Marplan for at least three weeks may have biased the analysis. Because of this, we requested that the company perform a cumulative (last observation carried forward) analysis of the data for all patients for five efficacy variables: physician rated Global Patient Improvement Scale, Covi Anxiety Scale total score, Hamilton Depression Scale total score, Hamilton Depression Scale depressed mood factor, and Hamilton Depression Scale retardation factor. This review describes the results of the cumulative analyses for the Giller study and the Davidson study.

I. Sponsor's Analysis

The Covi Anxiety Scale total score, Hamilton Depression Scale total score, Hamilton Depression Scale depressed mood factor, and Hamilton Depression Scale retardation factor were analyzed using an analysis of covariance with baseline score as a covariate. For the Giller study, time since diagnosis was included as an additional covariate. Because no baseline data was available for the Global Patient Improvement Scale, no covariates were used in the analysis of the Davidson study, and only time since diagnosis was used a covariate in the analysis of the Giller study. Each analysis was performed for weeks 1, 2 , 3 , 4 and 6 of the study. The following sections describe the results of these analyses.

A. Physician's Global Evaluation

Table 1 shows treatment means adjusted for the covariates used in the analysis (least squares means) and associated p-values for the Global Patient Improvement Scale.

Physician's Global Evaluation, Last Observation Carried Forward. Least Squares Means And P-Values From Sponsor's Analysis

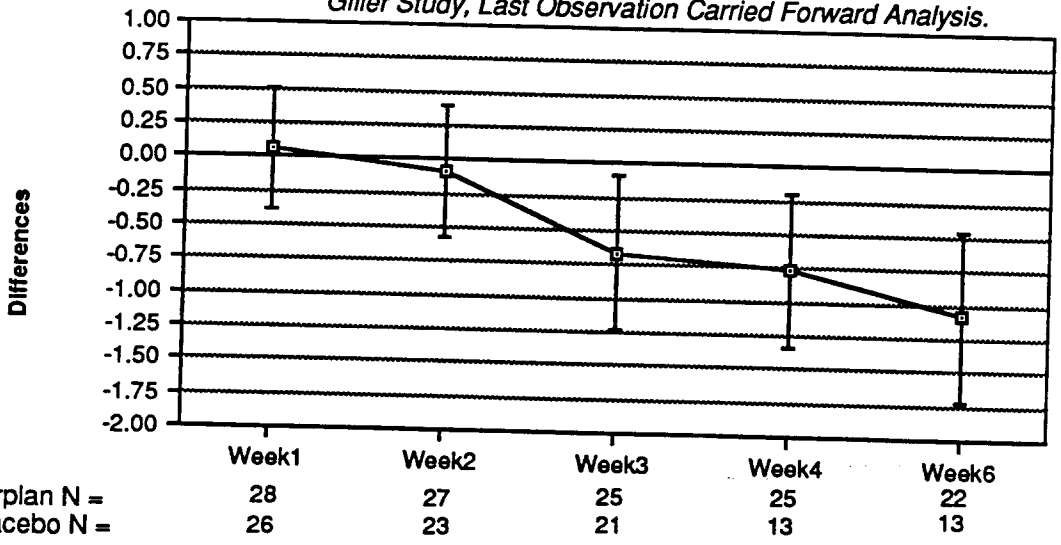
	Giller Study						Davidson Study					
	Marplan		*Placebo*		*Difference*		*Marplan*		*Placebo*		*Difference*	
	N	Mean	N	Mean	Mean	p-value	N	Mean	N	Mean	Mean	p-value
Week 1	28	3.81	26	3.75	0.1	.810	20	3.25	16	3.19	0.1	.849
Week 2	27	3.55	23	3.64	-0.1	.712	17	2.55	17	2.88	-0.3	.389
Week 3	25	3.16	21	3.82	-0.7	.031	16	2.20	14	2.94	-0.7	.085
Week 4	25	3.11	13	3.88	-0.8	.014	14	2.10	12	3.00	-0.9	.028
Week 6	22	2.66	13	3.75	-1.1	.002	11	2.00	9	2.76	-0.8	.073

Table 1

In the Giller study, Marplan is significantly different from placebo in weeks 3,4 and 6. In the Davidson study, it is significantly different from placebo in week 4. Figures 1 and 2 display the mean differences between Marplan and placebo and associated 95% confidence intervals.

Differences* Between Treatment Means And 95% Confidence Intervals For Global Evaluation.

Giller Study, Last Observation Carried Forward Analysis.



* Marplan least squares mean minus placebo least squares mean.

Figure 1

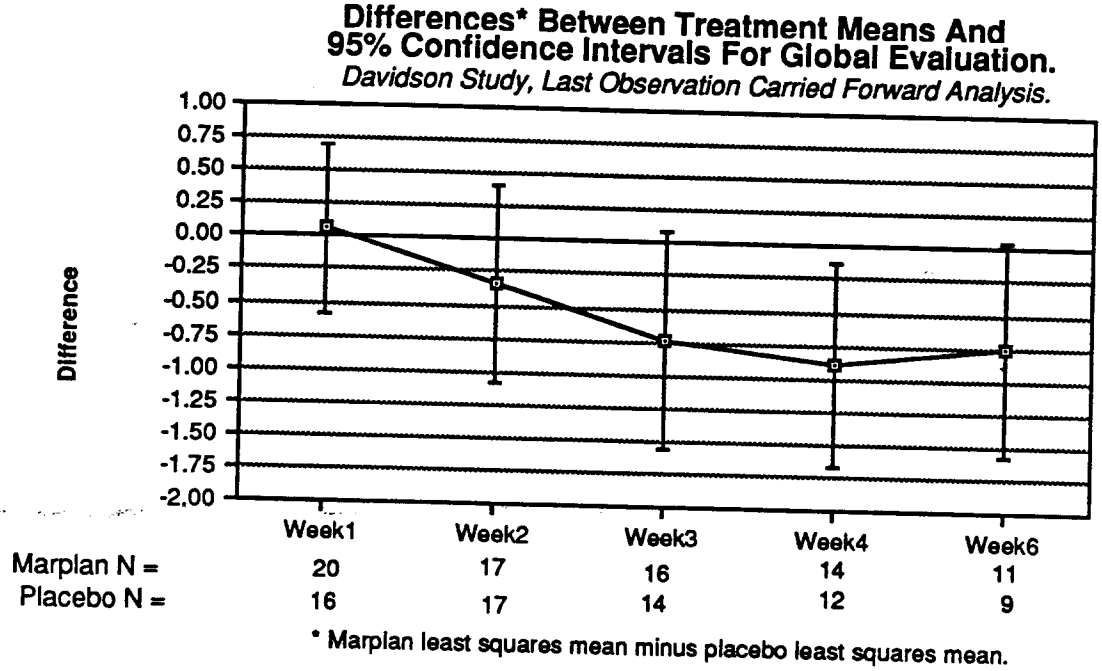


Figure 2

B. Hamilton Depression Scale- Depressed Mood Factor.

Table 2 shows treatment means adjusted for the covariates used in the analysis and associated p-values for the Hamilton Depression Scale depressed mood factor. In the Giller study, Marplan is significantly different from placebo in weeks 3,4 and 6. In the Davidson study, it is significantly different from placebo in weeks 4 and 6. Figures 1 and 2 display the mean differences between Marplan and placebo and associated 95% confidence intervals.

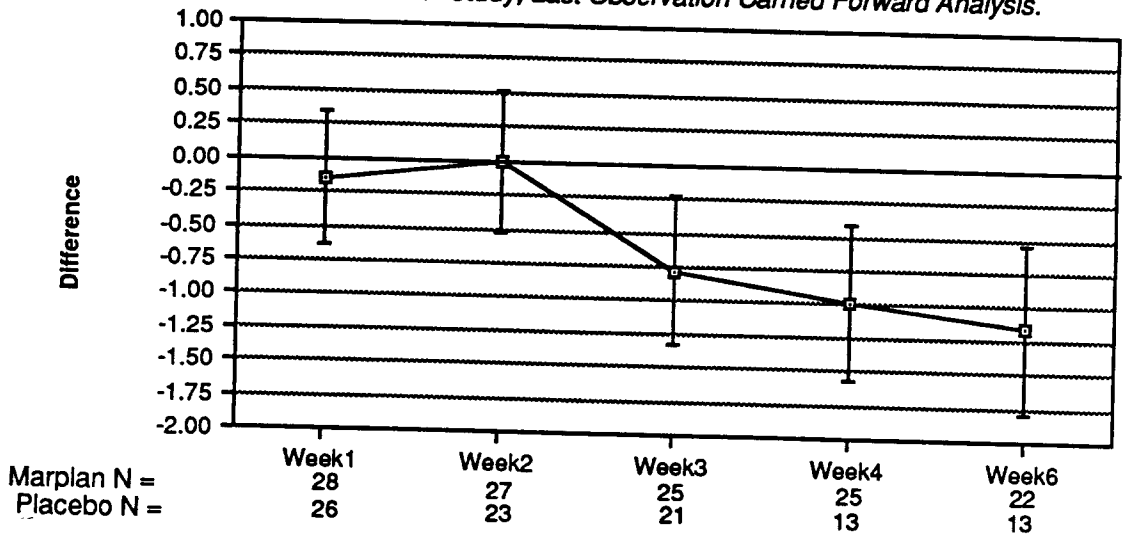
HD Depressed Mood Factor, Last Observation Carried Forward. Least Squares Means And P-Values From Sponsor's Analysis

	Giller Study						Davidson Study					
	Marplan		*Placebo*		*Difference*		*Marplan*		*Placebo*		*Difference*	
	N	Mean	N	Mean	Mean	p-value	N	Mean	N	Mean	Mean	p-value
Week 1	28	2.17	26	2.32	-0.2	.572	20	1.88	16	1.71	0.2	.563
Week 2	27	2.11	23	2.11	0.0	.987	17	1.17	17	1.63	-0.5	.206
Week 3	25	1.55	21	2.33	-0.8	.009	16	1.06	14	1.58	-0.5	.174
Week 4	25	1.39	13	2.39	-1.0	.002	14	0.73	12	1.79	-1.1	.007
Week 6	22	1.14	13	2.31	-1.2	.001	11	0.85	9	1.70	-0.9	.019

Table 2

Differences* Between Treatment Means And 95% Confidence Intervals For HD Depressed Mood Factor.

Giller Study, Last Observation Carried Forward Analysis.



* Marplan least squares mean minus placebo least squares mean.

Figure 3

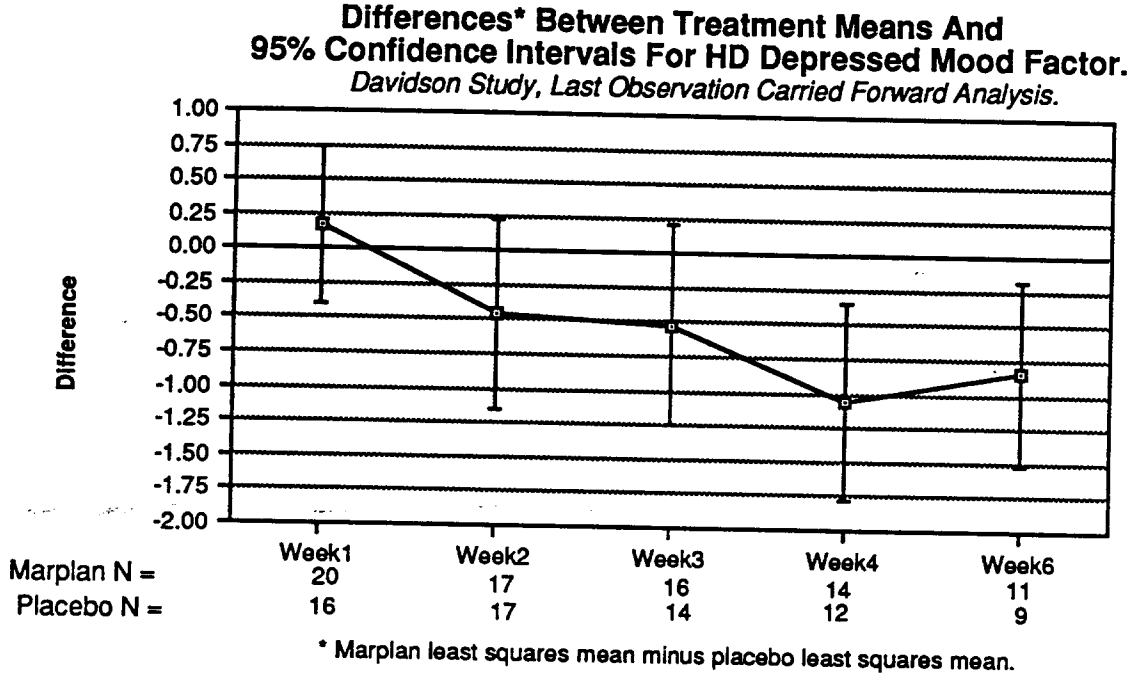


Figure 4

C. Hamilton Depression Scale- Retardation Factor.

Table 3 shows treatment means adjusted for the covariates used in the analysis and associated p-values for the Hamilton Depression Scale retardation factor. In the Giller study, Marplan is significantly different from placebo in week 6. In the Davidson study, it is significantly different from placebo in weeks 4 and 6. Figures 5 and 6 display the mean differences between Marplan and placebo and associated 95% confidence intervals.

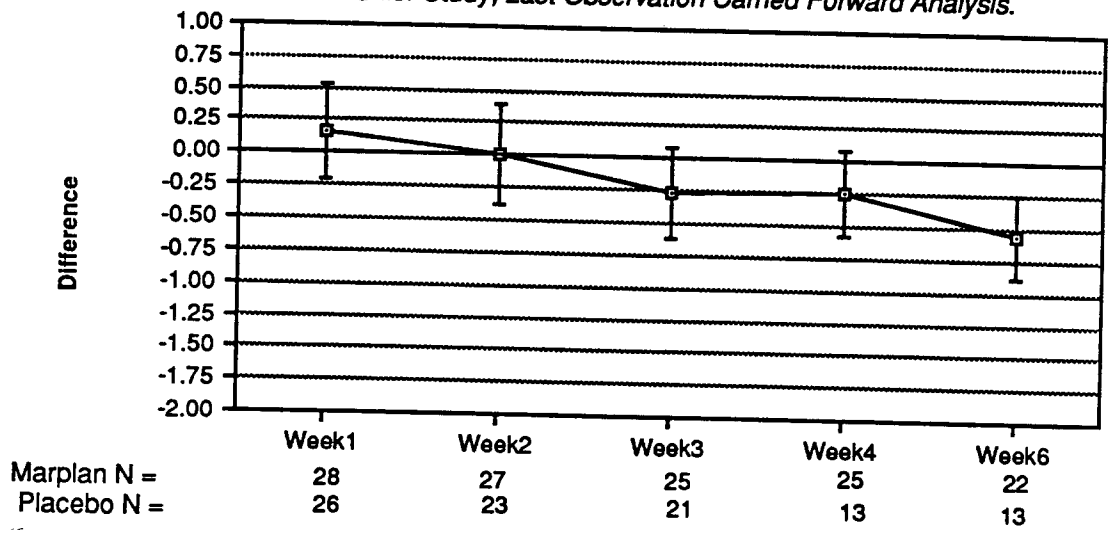
HD Retardation Factor, Last Observation Carried Forward. Least Squares Means And P-Values From Sponsor's Analysis

	Giller Study						Davidson Study					
	Marplan		*Placebo*		*Difference*		*Marplan*		*Placebo*		*Difference*	
	N	Mean	N	Mean	Mean	p-value	N	Mean	N	Mean	Mean	p-value
Week 1	28	1.08	26	0.91	0.2	.367	20	0.38	16	0.58	-0.2	.384
Week 2	27	0.74	23	0.74	0.0	.996	17	0.37	17	0.38	0.0	.968
Week 3	25	0.74	21	1.01	-0.3	.157	16	0.26	14	0.46	-0.2	.250
Week 4	25	0.55	13	0.80	-0.3	.155	14	0.04	12	0.72	-0.7	.000
Week 6	22	0.45	13	1.01	-0.6	.001	11	0.03	9	0.55	-0.5	.005

Table 3

Differences* Between Treatment Means And 95% Confidence Intervals For HD Retardation Factor.

Giller Study, Last Observation Carried Forward Analysis.



* Marplan least squares mean minus placebo least squares mean.

Figure 5

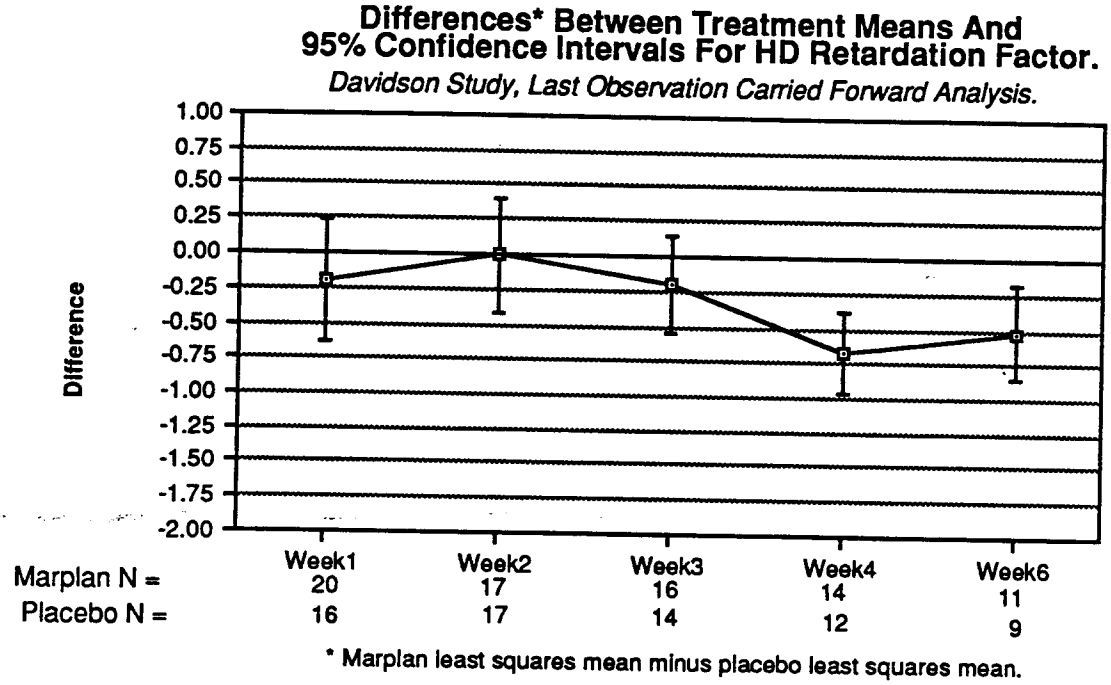


Figure 6

D. Hamilton Depression Scale- Total Score.

Table 4 shows treatment means adjusted for the covariates used in the analysis and associated p-values for the Hamilton Depression Scale total score.

HD Total Score Last Observation Carried Forward.
Least Squares Means And P-Values From Sponsor's Analysis

	Giller Study						Davidson Study					
	Marplan		*Placebo*		*Difference*		*Marplan*		*Placebo*		*Difference*	
	N	Mean	N	Mean	Mean	p-value	N	Mean	N	Mean	Mean	p-value
Week 1	28	27.23	26	28.48	-1.3	.585	20	22.21	16	20.79	1.4	.597
Week 2	27	25.75	23	26.01	-0.3	.919	17	15.88	17	18.14	-2.3	.548
Week 3	25	21.18	21	27.65	-6.5	.015	16	13.97	14	17.92	-4.0	.283
Week 4	25	19.77	13	26.90	-7.1	.013	14	11.96	12	19.63	-7.7	.043
Week 6	22	16.65	13	27.10	-10.5	.001	11	11.88	9	19.90	-8.0	.033

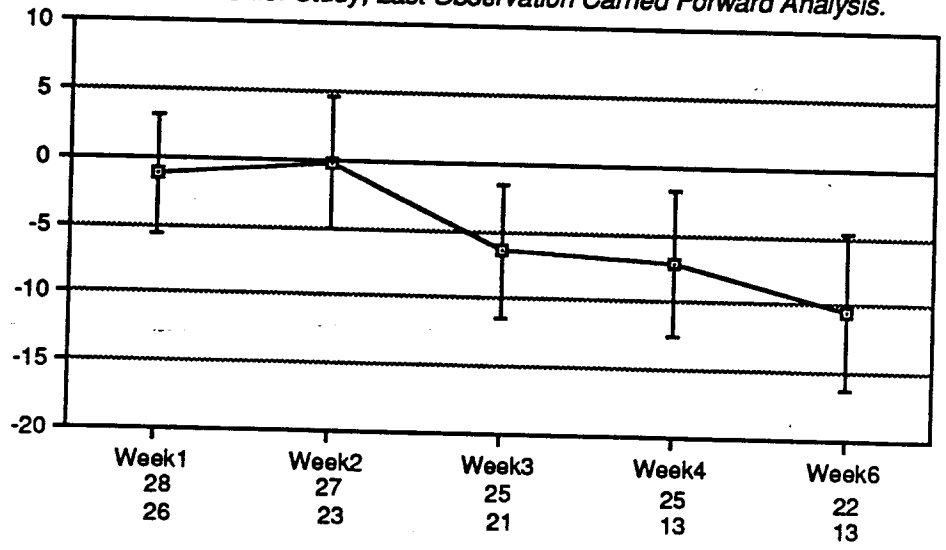
Table 4

In the Giller study, Marplan is significantly different from placebo in weeks 3, 4 and 6. In the Davidson study, it is significantly different from placebo in weeks 4 and 6. Figures 7

and 8 display the mean differences between Marplan and placebo and associated 95% confidence intervals.

Differences* Between Treatment Means And 95% Confidence Intervals For HD Total.

Giller Study, Last Observation Carried Forward Analysis.



	Week1	Week2	Week3	Week4	Week6
Marplan N =	28	27	25	25	22
Placebo N =	26	23	21	13	13

* Marplan least squares mean minus placebo least squares mean.

Figure 7

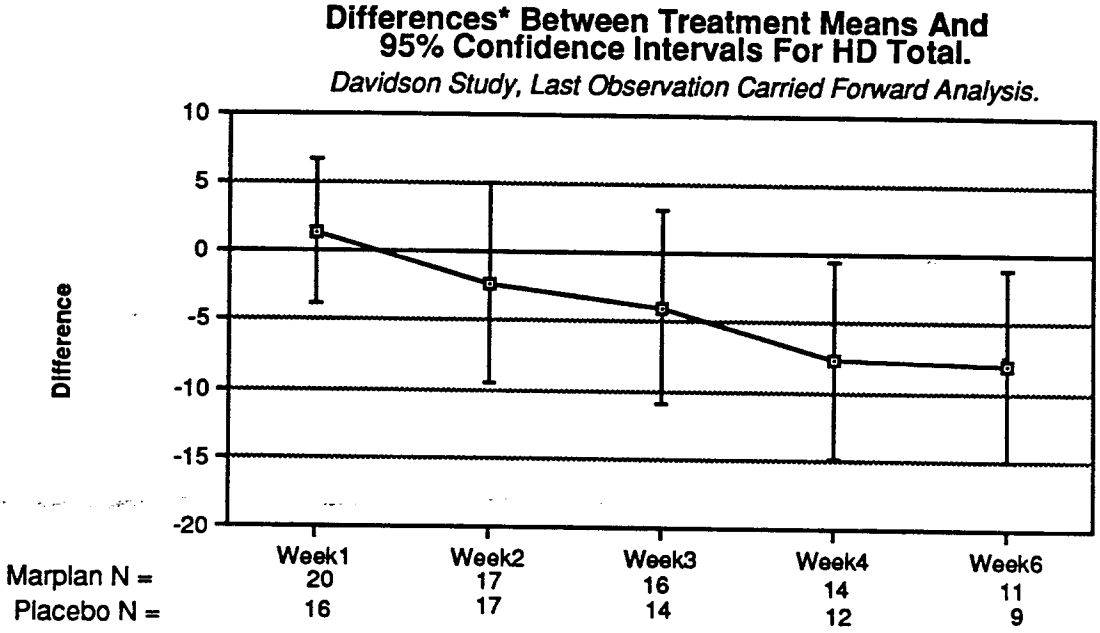


Figure 8

E. Covi Anxiety Scale.

Table 5 shows treatment means adjusted for the covariates used in the analysis and associated p-values for the Covi Anxiety Scale.

Least Squares Means And P-Values From Sponsor's Analysis COVI Anxiety Scale, Last Observation Carried Forward.

	Giller Study						Davidson Study					
	Marplan		*Placebo*		*Difference*		*Marplan*		*Placebo*		*Difference*	
	N	Mean	N	Mean	Mean	p-value	N	Mean	N	Mean	Mean	p-value
Week 1	28	8.7	26	8.6	0.1	.841	20	7.8	16	8.6	-0.8	.224
Week 2	27	7.9	23	8.4	-0.5	.445	17	6.6	17	7.2	-0.6	.470
Week 3	25	7.4	21	9.1	-1.7	.008	16	6.1	14	7.3	-1.2	.174
Week 4	25	6.9	13	9.0	-2.1	.001	14	5.8	12	7.3	-1.5	.114
Week 6	22	6.2	13	8.7	-2.5	.001	11	5.9	9	7.8	-2.0	.033

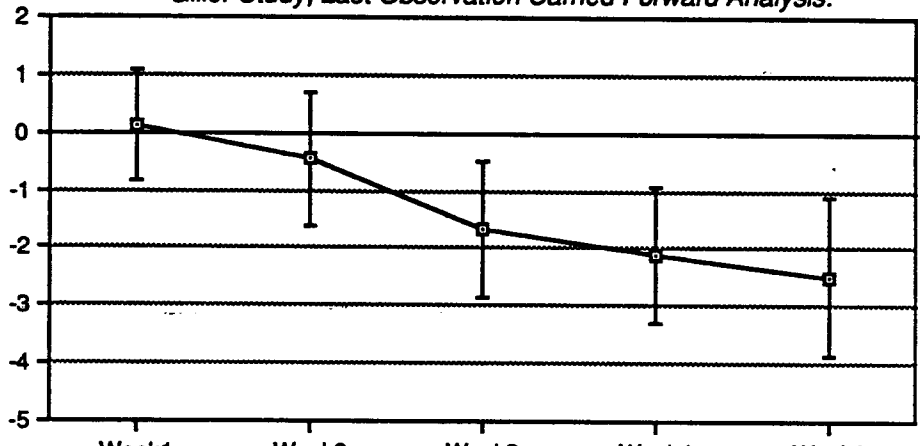
Table 5

In the Giller study, Marplan is significantly different from placebo in weeks 3, 4 and 6. In the Davidson study, it is significantly different from placebo in weeks 4 and 6. Figures 7

and 8 display the mean differences between Marplan and placebo and associated 95% confidence intervals.

Differences* Between Treatment Means And 95% Confidence Intervals For Covi Total.

Giller Study, Last Observation Carried Forward Analysis.



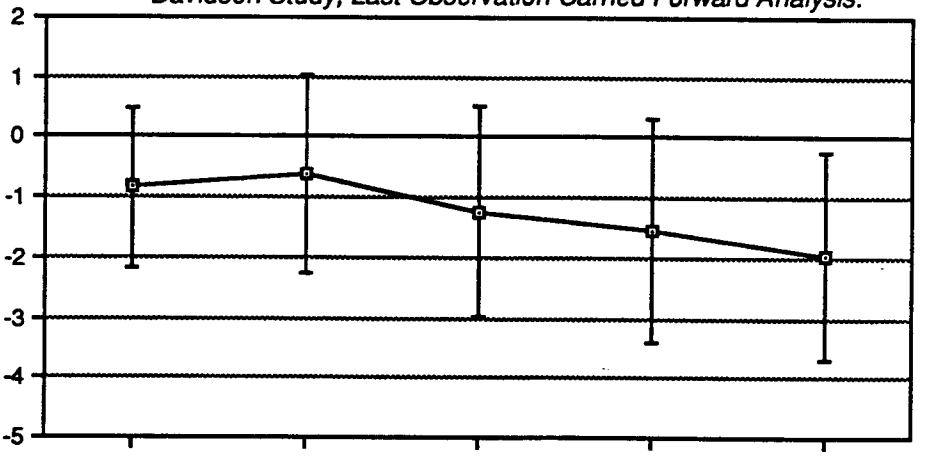
	Week1	Week2	Week3	Week4	Week6
Marplan N =	28	27	25	25	22
Placebo N =	26	23	21	13	13

* Marplan least squares mean minus placebo least squares mean.

Figure 9

Differences* Between Treatment Means And 95% Confidence Intervals For Covi Total.

Davidson Study, Last Observation Carried Forward Analysis.



	Week1	Week2	Week3	Week4	Week6
Marplan N =	20	17	16	14	11
Placebo N =	16	17	14	12	9

* Marplan least squares mean minus placebo least squares mean.

Figure 10

cc:
Orig. NDA 19-302 ✓
HFN-120
HFN-120/Mr. DeCicco
HFN-120/Dr. Leber
HFN-120/Dr. Laughren
HFN-713/Dr. Dubey[File: DRU 1.3.2]
HFN-713/Mr. Levine
HFN-344/Dr. Lisook
Chron
This review consists of 12 pages.
JGL/November 9,1987/Microsoft Word 3.01

II. Reviewer's Comments

The Giller study provides compelling statistical evidence that Marplan reduces patient's scores for the physician rated Global Patient Improvement Scale, Covi Anxiety Scale total score, Hamilton Depression Scale total score, and Hamilton Depression Scale depressed mood factor after three weeks of therapy. Statistically significant reductions in Hamilton Depression Scale retardation factor were not observed until the sixth week.

The results of the Davidson study are not as convincing, but still indicate a drug effect. The Davidson study provides statistical evidence that Marplan reduces patient's scores for the physician rated Global Patient Improvement Scale, Hamilton Depression Scale retardation factor, Hamilton Depression Scale total score, and Hamilton Depression Scale depressed mood factor after four weeks of therapy.

A final comment has to do with the dosage recommended by the sponsor in the package insert. Although 54% (15/28) of the patients in the Giller study and 55% (11/20) received dosages greater than 50 mg/day during the course of the study, the sponsor recommends a maximum dose of 50mg/day. In light of the large number of patients receiving dosages greater than 50mg/day, it is not reasonable to assume that the results of the study would have been the same had no patients received dosages greater than 50mg/day. A maximum dose which would be more consistent with the dosages used in this study would be 60mg/day, since only one patient (4%) in the Giller study and five patients (25%) ever received a dose greater than 60mg/day.

/S/ 11/9/87

~~Jonathan Levine, M.S~~

Mathematical Statistician

Concur:

Dr. Nevius /S/ 11/16/87

Dr. Dubey /S/ 11-19-87

FEB 26 1996

NDA 11-961/S-017

Hoffmann-La Roche Inc.
Attention: Anthony Corrado
Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Mr. Corrado:

Please refer to your supplemental New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marplan® (isocarboxazid) tablets dated August 28, 1981, and amended on October 22, 1987, October 27, 1987, December 16, 1988, and October 27, 1995.

Reference is also made to an Agency letter dated June 24, 1988, not approving this supplemental application, and to an Agency letter dated April 14, 1994, acknowledging that Hoffmann-La Roche has voluntarily withdrawn Marplan® from the marketplace.

The supplemental application provides for safety and efficacy data from three adequate and well controlled studies in support of a claim for the effectiveness of Marplan® in the treatment of patients with atypical depression. We note that this supplement was submitted as part of a DESI submission.

We have completed our review of your resubmission, including the reanalyzed efficacy data and the retrospective analysis of the postmarketing safety data base, and we find that the information presented is adequate and the application is now approvable.

Although the supplement is now approvable, there are several issues that need to be addressed before this application can be finally approved. (1) Although we believe there are sufficient data to permit the marketing of Marplan® at the higher doses now recommended, we continue to believe there are important gaps in the knowledge base for this drug. Although we acknowledge that you have now provided sufficient data to support the effectiveness of Marplan® in the acute treatment of non-endogenous depression in a dose range of up to 60 mg/day, you have not addressed the question of dose/response for the efficacy of Marplan® in the dose range of 30 to 60 mg/day. In addition, it continues to be our view that you have not yet provided sufficient data regarding the safety of Marplan® in order to fully inform clinicians about the incidence of adverse events in the dose range that is now being recommended. Consequently, we ask that, as a condition of approval, you commit to conducting additional studies post-approval to address these deficiencies. (2) The labeling for Marplan® is also deficient, and we have provided comments below regarding what is needed to repair the labeling for this product. (3) Finally, we have commented below on what we consider to be an appropriate response on your part to the continuing need for Marplan® by current users during this time interval before the supplement can be finally approved.

1 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

Repair of Labeling for Marplan

If Marplan is to be approved at the higher recommended maximum dose, the labeling needs considerable work. Marplan• labeling is not in the currently accepted format, and as a first step, we ask that you rewrite the labeling to conform to the currently accepted format and content guidelines. In addition, we have more specific requirements for selected sections of the labeling:

CLINICAL PHARMACOLOGY: This section is currently identified as "Actions," and contains much information that either doesn't belong in labeling at all or belongs elsewhere in labeling. The LD50 and other animal toxicology data can be deleted from labeling. The reproduction data can be moved to the appropriate subsection of **PRECAUTIONS**. The revised **CLINICAL PHARMACOLOGY** section should have three subsections, i.e., **Pharmacodynamics**, **Pharmacokinetics**, and **Clinical Trials**. The pharmacology of isocarboxazid should be summarized under **Pharmacodynamics**. You need to summarize what is known from the literature or other sources about the pharmacokinetics of isocarboxazid under **Pharmacokinetics**. Finally, the results from the two positive Giller and Davidson studies need to be summarized under a **Clinical Trials** subsection.

INDICATIONS AND USAGE: You have proposed that Marplan• be indicated as follows:

> "patients suffering from atypical depression, a condition characterized by dysphoric mood, fatigue, anxiety and somatic complaints. Many of these patients have a history of phobic and/or panic symptoms; endogenous features are not usually prominent."

We cannot agree with an indication for "atypical depression" since there is no consensus regarding a definition for atypical depression. As an alternative, we have proposed a claim consistent with the population actually recruited in your studies supporting the effectiveness of Marplan•. In addition, we have proposed labeling language recommending that (1) Marplan• not be considered a first line drug, as is the case for the only other 2 MAOIs approved for depression; (2) Marplan• has not been adequately studied in hospitalized depressed patients; and (3) the long-term effectiveness of Marplan• has not been adequately studied.

We ask that you adopt the following language for this section:

> "Marplan• is indicated for the treatment of depression.
>
> The efficacy of Marplan• in the treatment of depression was established in 6-week controlled trials of depressed outpatients. These patients had symptoms that corresponded to the DSM-IV category of major depressive disorder, however, they often also had signs and symptoms of anxiety (anxious mood, panic, and/or phobic symptoms).
>
> A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings

of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of Marplan® in hospitalized depressed patients, or in endogenomorphically retarded and delusionally depressed patients, has not been adequately studied.

For these reasons, and because of the potentially serious consequences of its side effect profile, Marplan® is not to be considered as an antidepressant of first choice in the treatment of newly diagnosed depressed patients with prominent endogenous features.

The effectiveness of Marplan® in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Marplan® for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient."

ADVERSE REACTIONS: This section is deficient in that it provides no quantitative information regarding incidence of adverse events and no dose/response information. The repair of these deficiencies will be corrected in part through additional studies, as suggested above. In the meantime, this section would be much improved by the addition of data pooled from your three placebo controlled studies (Giller, Davidson, and Zisook). Included should be a table providing adverse events occurring at an incidence of $\geq$ 1% for Marplan®. In addition, although recognizing the difficulty in trying to examine dose/response from titration studies, some attempt should be made to explore for dose/response. The revised section should emphasize the sparseness of the systematically collected adverse event data for this drug, e.g., by including a statement noting that systematically collected data are available from only 87 patients exposed to Marplan®, of whom only 66 received doses of $\geq$ 50 mg/day, including only 35 who were dosed at $\geq$ 60 mg/day. Given the limitations on the available data, labeling should include in this section a statement advising particular caution in patients for whom a dose of 40 mg/day is exceeded, with a reference to Warnings where this cautionary language will need to be repeated.

WARNINGS: As noted, this section should include a statement warning clinicians about the limitations on the safety experience with Marplan® at the higher end of the recommended dose range. We suggest that the following statement be added after the first paragraph in the current Warnings section: "Because of the limited experience with systematically monitored patients receiving Marplan® at the higher end of the currently recommended dose range of up to 60 mg/day, caution is indicated in patients for whom a dose of 40 mg/day is exceeded (see Adverse Reactions)."

DOSAGE AND ADMINISTRATION: This section should also include a statement emphasizing the need for particular caution when exceeding doses of 40 mg/day, given the sparseness of systematically collected adverse event data at higher doses.

<u>Current Status of Marplan</u>

On March 31, 1994, you notified the Agency that you would no longer market Marplan®. Apparently, this decision resulted in a number of requests to you from patients and physicians to keep Marplan® on the

market. You have subsequently and are currently providing Marplan® at no cost to physicians for patients who need this drug. We understand that you consider this a temporary measure, and that you do not plan to produce more product once the current supplies are exhausted (estimated date about March, 1996).

Given that this supplement is now approvable, it is our hope that you will continue to provide Marplan® under your limited distribution program.

Should you have any questions concerning this supplemental application, please contact Mr. Paul A. David, Regulatory Management Officer, at (301) 594-2777.

Sincerely yours,

/S/ 2/22/96

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

cc:
NDA ORIG 11-961 /S/ 12-9-96
HFD-120/DIV File
HFD-101/LCarter
HFD-120/PLeber/TI[illegible]ren/GFitzgerald/EHearst
HFD-120/PDavid /S/ 2-8-96
HFD-007/DSullivan-Ford
rd:12/28/95pd
rev:12/29/95tl; 1/31//96tl; 2/13/96 /S/
ft:02/08/96pd
Doc #N:\DAVID\LTRMRPLN.AE1 /S/ 2/23/96

DESI SUPPLEMENT APPROVABLE

NDA 11-961

APR 14 1994

Hoffmann-La Roche Inc.
Attention: Anthony Corrado
Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Mr. Corrado:

Please refer to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marplan® (isocarboxazid) tablets.

We acknowledge receipt of your communication dated March 31, 1994, notifying the Agency that you have discontinued marketing of this drug. Additionally, we note that you intend to supply individual physicians with Marplan® tablets on a case-by-case basis to assist physicians in slowly weaning their patients off this drug.

If you decide to market this drug product again at some future date, this Agency should be notified prior to such action.

Sincerely yours,

/S/

4/11/94

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Orig NDA
HFD-120/Div file
HFD-53
HFD-120/PLeber/TLaughren/EHears
HFD-120/GFitzgerald/PDavi
HFD-120/RShultz/WBrannon
ACKNOWLEDGE MARKETING BEING DISCONTINUED

/S/ 4-8-94 /S/ 4/8/94

/S/ 4/7/94

Dual off.

DN file
120

REGISTERED MAIL
RETURN RECEIPT REQUESTED

JUN 24 1988

NDA 11-961/S-017

Hoffman-La Roche Laboratories
Attention: Peggy Jack
Nutley, New Jersey 07110

Dear Ms. Jack:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Marplan^{R} (isocarboxazid) tablets.

We also acknowledge receipt of the following submissions:

August 28, 1981
October 11, 1982
October 22, 1987
October 27, 1987

This supplemental application provides data from three adequate and well controlled studies in support of a claim for the effectiveness of Marplan in the treatment of patients with atypical depression.

We have completed our review of this supplemental submission (S-017) and find that the information presented is inadequate and the application is not approvable.

You have partially met the requirements stated in the July 14, 1978 Federal Register notice for keeping Marplan on the market, in that you have conducted two adequate and well controlled studies that demonstrate the antidepressant efficacy of Marplan. We believe that the Davidson and Giller studies are positive, while the Zisook study is not. However, Marplan was administered at doses up to 80 mg/day in both the Davidson and Giller studies, a dose far exceeding the maximum dose of 30 mg/day recommended in currently approved labeling for Marplan.

We note that in your October 22, 1987 amendment you have recommended a maximum dose of 50 mg/day in your labeling proposal. Since 11 of the 22 patients assigned to Marplan in the Davidson study and 15 of the 30 patients assigned to Marplan in the Giller study received Marplan doses greater than 50 mg during at least part of the trial, we do not agree with this maximum dose recommendation. Since only one patient assigned to Marplan in the Giller study received a dose greater than 60 mg/day, this study would support a maximum dose recommendation of 60 mg/day. However, this is not true of the Davidson study, in which five Marplan patients received doses greater than 60 mg/day during their participation in that trial.

You might consider reanalyzing the Davidson study after excluding the five subjects who received doses greater than 60mg/day, in order to provide adequate support for a recommendation of a maximum dose of 60 mg/day in the labeling. Alternatively, you would need to conduct an additional study. We would strongly recommend a three-way study comparing Marplan (at doses not exceeding 60 mg/day), a standard tricyclic antidepressant and placebo. The third treatment arm is not essential, but may provide additional information about the patient sample and its responsiveness to traditional antidepressants. However you choose to resolve this issue, you need to provide adequate support for the effectiveness of the dose range to be recommended in labeling. Based on currently available data, we would only be willing to accept a maximum dose recommendation of 80 mg/day.

Once the issue of maximum recommended dose is resolved from the standpoint of efficacy, the issue of safety needs to be addressed. Whether the maximum recommended dose ultimately agreed upon is 60 or 80 mg/day, the safety data you have provided are insufficient. While nothing catastrophic happened to the patients who received Marplan in your studies, only 87 patients actually received Marplan, and an even smaller number received Marplan at the higher doses in the permitted dose range. We cannot rely on this small sample of data as a basis for establishing the safety of a maximum recommended dose of 60 or 80 mg/day.

Consequently, you need to obtain additional safety experience in the recommended dose range, once this range is established. For a maximum recommended dose of 80 mg/day, we would want at least 1000 additional patients treated with Marplan at doses ranging up to a maximum dose of 80 mg/day, including several hundred receiving doses at the higher end of the permitted dose range. These data could be obtained in an open study.

Should you wish to conduct additional clinical trials, Division of Neuropharmacological Drug Products staff would be happy to meet with you to discuss the design of such studies.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other actions under 21 CFR 314.120. In the absence of such action, FDA may take action to withdraw the application.

Should you have any questions please contact Mr. Tony DeCicco, Consumer Safety Officer at (301) 443-3504.

Sincerely yours,

/S/

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

NDA/IND ORIG.
HFD-83
HFD-85
HFD-10 /S/ 6/17/88
HFD-12 /S/ 6-17-88
HFD-120/Leber/Laugnren
HFD-120/DeCicco
HFD-713/~~Nevius~~/Levine
rd/ad/5/3/88
ft/ad/5/3/88/5/10/88/5/24/88

Doc 2814c

DUPLICATE

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-562-3698
Fax 201-562-3700

SUPPL AMEND
SE1-017
(AM)

April 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 05 1997
HFD-120

Robert Temple, M.D., Director
Office of Drug Evaluation I
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-101)
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 11-961 (S017)
Marplan® (isocarboxazid) Tablets - DESI Submission

Dear Dr. Temple:

Reference is made to the supplemental New Drug Application for Marplan® (iscarboxazid) tablets which was originally submitted as part of a DESI submission on August 28, 1981 and amended on October 22, 1987, October 27, 1987, December 16, 1988 and October 27, 1995. Subsequent to the last amended submission, Hoffmann-La Roche Inc. (Roche) received an FDA Approvable letter dated February 26, 1996

Approvable letter outlining the recommendations proposed by the FDA to resolve the DESI status for this product.

We trust that the information provided herein addresses the Agency's issues related to the supplemental NDA for Marplan®. Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

Anthony J. Corrado
Associate Director
Drug Regulatory Affairs

AJC/lmh
Attachments
HLR No. 1997-964

Desk Copy: Mr. Paul David, Project Management Staff
Division of Neuropharmacological Drug Products
HFD-120

ORIGINAL

NDA NO. 11-961 REF. NO. SLR-0

NDA SUPPL FOR Draft Lab

Roche Pharmaceuticals

A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3698
Fax (201) 812-3700/3554

NDA SUPPL AMEND

SE1-017(AM)

This correspondence should be placed with S-0... DDR notified of change. Roche notified of change. /S/ 12-28

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 30 1995
HFD-120

October 27, 1995

Food and Drug Administration
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Woodmont II Building
1451 Rockville Pike
Rockville, Maryland 20852

Ladies and Gentlemen:

Re: Marplan® (isocarboxazid) Tablets - NDA 11-961 (S-017)

Reference is made to a November 28, 1994 Supplement (S-017) which in part included a summary of the background information for an outstanding Marplan® Tablets DESI issue. Within this summary, Hoffmann-La Roche Inc. requested an opportunity to discuss, in a meeting with the FDA, the need to resolve this DESI issue

One of the concerns surrounding this DESI issue was a recommendation made by the FDA in a June 1988 letter (Attachment 2), in which an in-depth safety study should be conducted in at least 1000 patients, once a maximum dosage for efficacy was agreed upon (60 mg/day was proposed by Hoffmann-La Roche Inc.). A study of this size (1000 patients), would not only incur a tremendous resource issue, but at this time may even exceed the total patient population for this study.

Also included in this Supplement for review, is a Marplan® draft package insert providing revisions to the **INDICATIONS** and **DOSAGE and ADMINISTRATION** sections reflecting both the reanalyzes of our efficacy studies, previously submitted to the Agency, and the results of the retrospective analysis (Attachment 4).

Recently, the Division of Regulatory Policy informed Hoffmann-La Roche Inc. of their need to resolve any outstanding DESI concerns for Marplan® and the expected time frame in which to do so. We are hopeful this submission will provide sufficient data to permit the approval of Marplan® in accord with the enclosed draft package insert. In the event you believe this information is not sufficient for approval of the Marplan® package insert, Hoffmann-La Roche Inc. requests the opportunity to discuss this matter with the Neuropharmacology Division at your earliest possible convenience.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Senior Manager
Drug Regulatory Affairs

dmb
Attachments
NDA No. 1995-1841
Desk Copy: Mr. Paul David (CSO, Neuropharmacology Division)

S-017
NDA [illegible] AMEND...

ROCHE **Hoffmann-La Roche**

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-235-4692

December 16, 1988

11-30-91
Sponsor has not yet submitted safety data. Will review efficacy data only when all required data re. submitted /S/

Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Attn: DOCUMENT CONTROL ROOM 10B-30
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Marplan (isocarboxazid) Tablets - NDA 11-961

Reference is made to the Agency's non-approvable letter dated June 24, 1988 for supplemental submission S-017 for the above-mentioned product and Hoffmann-La Roche's letter of July 1, 1988 indicating our intent to amend this application.

We are herewith amending this application and submitting a statistical reanalysis of the efficacy data for the Davidson Study as per your June 24, 1988 letter. This reanalysis excludes patients in the Davidson Study who received Marplan doses of 80 mg/day and substantiates the efficacy of Marplan for atypical depression at doses up to 60 mg/day in that study.

In response to your concerns about insufficient safety data for Marplan at doses in the recommended dose range, we are currently reviewing all clinical data available for this product including clinical studies, postmarketing experience, published literature and data on file in order to assess the currently available safety information. Once this review is complete, we intend to request a meeting with the Agency to discuss if and what additional safety information is necessary for this application.

If you have any additional questions concerning this submission, please contact the undersigned at 201-235-4692.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Manager,
DRA and Data Services
Drug Regulatory Affairs

MJJ/cs
Attachment
HLR No. 88908

0216

NDA SUPPL AMENDMENT
SES 017 BN

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY • 07110

Drug Regulatory Affairs
(201) 235-5000

October 27, 1987

Division of Neuropharmacological Drug Products
Bureau of Drugs, HFD-120
Attn: DOCUMENT CONTROL ROOM 10B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: **MARPLAN (isocarboxazid) Tablets - NDA 11-961**

Reference is made to our submission dated October 22, 1987 and our telephone conversation on October 26, 1987 concerning that submission for the above mentioned NDA. We are herewith submitting, as requested, the tables containing the average dose for specified time intervals of Marplan and placebo administered to each patient in the Giller and Davidson studies during the time course of the respective studies.

Tables 1 through 4 for the Giller and Davidson studies were pages 93, 94, 40 and 41 respectively of Volume 1 of the DESI submission dated August 28, 1981. These are included herein for the convenience of the reviewer.

Tables 5 through 8 for the Giller and Davidson studies have not been previously submitted.

Tables 1 through 4 differ from Tables 5 through 8 in the following manner:

1. The specified dosage intervals are different.

Dosage Interval	Tables 1 - 4 (Interval in Days)	Tables 5 - 8 (Interval in Days)
Week 1	1	-
2	2 - 10	3 - 10
3	11 - 17	11 - 17
4	18 - 24	18 - 24
5	25 - 35	25 - 35
6	36 - 51	36 - 51

2. The Giller Study reported in Tables 5 and 6 include 3 additional patients, patient # 60 on Marplan and patients #'s 58 and 59 on Placebo.

In addition, we are resubmitting Table 6 of Volume 1 of the October 22, 1987 submission. The original Table 6 had a typographical error which has now been corrected.

Please feel free to contact the undersigned if you have any further questions concerning this submission.

Sincerely,

HOFFMANN - LA ROCHE, INC.

Margaret Jack

Margaret J. Jack
Manager, DRA & Data Services
Drug Regulatory Affairs
201/235-4692

MJJ:fp
MLR No. 87955
Attachments
Desk Copy - Thomas Laughren, M.D.

ORIGINAL

NDA SUPPL AMENDMENT

S-017

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY • 07110

Drug Regulatory Affairs
(201) 235-5000

October 22, 1987

Division of Neuropharmacological Drug Products
Bureau of Drugs, HFD-120
Attn: DOCUMENT CONTROL ROOM 10B-30
5600 Fishers Lane
Rockville, Maryland 20857

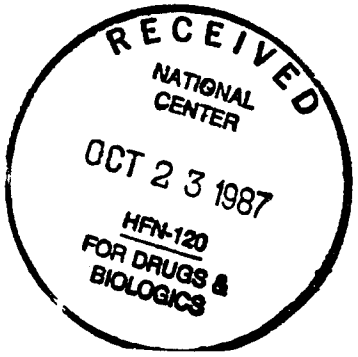
Gentlemen:

Re: **MARPLAN (isocarboxazid) TABLETS - NDA 11-961**

Reference is made to the teleconference held on July 13, 1987 between FDA and representatives of Hoffmann-La Roche Inc. to discuss the DESI submission dated August 28, 1981 for the above-mentioned NDA. During the teleconference FDA requested statistical reanalysis of portions of the aforementioned DESI submission.

We are herewith submitting the statistical reanalysis as requested. This submission includes:

- Summary depicting the methodology and results of the statistical reanalysis.
- As per our agreement in the July 13, 1987 teleconference, the SAS printout of the following is also included:
  - i. Reanalysis of two studies (Davidson and Giller) in the DESI submission based on the "intent to treat" analysis.
  - ii. Reanalysis with duration of depression as an additional covariate in the Giller study.
  - iii. Reanalysis of the standard (observed cases) and cumulative analysis for each week of the study.



Also included in this submission is the revised draft package insert. The DOSAGE AND ADMINISTRATION section of the package insert, previously included in the August 28, 1981 submission, has been revised to now include a maximum daily dosage recommendation of 50 mg/day.

This submission to the NDA is organized as follows:

Volume 1	- Cover Letter, Summary of Methodology and Results and Revised Draft Package Insert
Volume 2	- Statistical Analysis of the Giller and Davidson Studies for Evaluable Patients and Individual Patient Data listings
Volume 3	- Statistical Analysis of the Giller and Davidson Studies for Intent to Treat and Individual Patient Data listings
Volume 4	- Safety Data Including Adverse Drug Experience and Abnormal Laboratory Test Results

This submission is also referenced to IND 13,441 under which these studies were conducted and to which the protocols for these studies were submitted.

Your timely review of this submission would be greatly appreciated.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Manager, DRA and
Data Services
Drug Regulatory Affairs
(201) 235-4692

MJJ/cas
Attachment

HLR No. 87940

ORIG

PARAGRAPH XIV DRUGS
CATEGORY XX ISOCARBOXAZID
NDA NO. 11-961 REF. NO. S-01

HOFFMANN-LA ROCHE INC. NDA SUPPL FOR EFFICACY SUPP.

NUTLEY • NEW JERSEY • 07110

August 28, 1981

Division of Neuropharmacological
Drug Products
Bureau of Drugs, HFD-120
Attn: DOCUMENT CONTROL ROOM 10B-30
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: MARPLAN (isocarboxazid) TABLETS
NDA 11-961
Supplement to NDA
44 F.R. 50409

Reference is made to the Federal Register notice published on July 14, 1978, which announced the conditions under which isocarboxazid tablets could remain on the market pending the completion and review of clinical studies to determine its effectiveness in the treatment of depression. Reference is also made to the Federal Register notice published on August 28, 1979, which amended the July 1978 notice and reestablished the deadline date for submission of data on the completed clinical studies.

Submitted herewith are the reports of three clinical studies which demonstrate the effectiveness of Marplan in the treatment of atypical depression.

This supplement to the NDA is organized as follows:

Volume 1	Summaries, Individual Study Reports, Revised Draft Package Insert, Location of Documents (in triplicate)
Volumes 2, 3, 4	Statistical Analysis of each study (in triplicate)
Volume 5	Protocols, Curricula Vitae, Drug Codes, Laboratory Values (in triplicate)
Volume 6	Forms FD 1639 (in duplicate)
Volumes 7-30	Case Reports (ribbon copy only)

RECEIVED
AUG 27 1981
HFD-120
BUREAU OF DRUGS

August 28, 1981

This submission is also referenced to IND under which these studies were conducted and to which the protocols for these studies were submitted.

Sincerely,

HOFFMANN-LA ROCHE INC.

Karen K. Church

Karen K. Church
Assistant Director
Drug Regulatory Affairs

KKC:ki
Enclosure
Form FD 356H

M E M O R A N D U M

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

DATE: MAY 18 1988

FROM: Director, Office of Drug Evaluation I, HFD-100

SUBJECT: Marplan^R, NDA 11-961/S-017

TO: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

The Marplan^R outcome certainly represents an interesting regulatory problem. As you note in your memo, we will need to decide what to do about its marketing status. Before we get to that point, however, I would like to explore some additional options.

1. Regarding the dose that would need to be recommended, it does not seem to me that we are necessarily obliged to conclude that it must be 80 mg and that reanalysis of the Davidson study is out of the question. We have two studies that demonstrate that Marplan^R is an effective antidepressant. It is not, I believe, necessary that there be two studies demonstrating every aspect of that effectiveness. Thus, the fact that the Giller study can be interpreted as showing that 60 mg is an effective dose leads me to think that we might consider an exception to our usual (very well founded) rule that such practices as excluding the high dose patients from the Richardson study and carrying out an analysis of the remainder would not be acceptable. I think this is especially true when we know from Dr. Laughren's evaluation that, if anything, those excluded patients did particularly well, not particularly poorly, so that excluding them will not produce a bias favoring the drug. This will not solve our entire problem, of course, as we do not have adequate safety data even for 60 mg, but it might make it unnecessary to carry out an additional randomized trial. I should note parenthetically that the difference between 60 mg and 80 mg is not very large and that it would be unlikely, especially given the results in the Giller study, that the effectiveness of Marplan^R depends on reaching the 80 mg dose and that there is no effectiveness at 60 mg.

2. The safety issue raised by the need to use a larger dose than recommended is a novel one, I believe, and I recall only one similar situation under DESI; dicyclomine was approved for treatment of irritable bowel syndrome at a dose higher than that previously recommended. It was quite clear that the drug was relatively poorly tolerated at this dose although the intolerance did not pose serious risks, and the larger question of overall safety was not raised. I have some concern that in seeking data on a thousand patients we will be setting a task that Roche will be unwilling to meet and we will be faced with the loss of what appears to be a useful agent.

Therefore, it seems to me we should explore some possible alternative ways of gaining additional safety data. First, it ought to be possible to determine what dose of Marplan^{R} is actually being used in the community. If we were to discover that most, or many people were using doses well above 30 mg, we might find that the marketing history would provide acceptable evidence that the drug is well tolerated at the larger dose. If, on the other hand, everyone is in fact using 30 mg or less we will not be able to take any such comfort. It also seems probable to me that over the years there have been a reasonable number of studies, not necessarily controlled trials, that have used Marplan^{R} at larger doses and Roche ought to be invited to sift through those data to see if they can provide pertinent information. Finally, I think we should discuss whether our requested safety data base needs to be as large as a thousand patients. We do, after all, know something about this drug and I am not sure it should be approached as if it were a drug that had never been marketed before. I acknowledge, however, that the substantial increase in dose does give it elements of a new molecular entity.

/S/

Robert Temple, M.D.

cc:
Orig. NDA 11-961
HFD-100/Chron File
HFD-100/Drug File
HFD-100/NDA File
HFD-101/Botstein
HFD-120/CSO
RT:jp:5/16/88:Wang #2345d
Revised:RT:jp:5/18/88(2)