CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020720/S002,S003,S005

TRADE NAME: Rezulin 200 mg and 400 mg Tablets

GENERIC NAME: Troglitazone

SPONSOR: Parke Davis Pharmaceutical Research

APPROVAL DATE: 08/04/97

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-720/S-002
NDA 20-720/S-003
NDA 20-720/S-005

AUG 4 1997

Parke Davis Pharmaceutical Research
Attention: Mary E. Taylor, M.P.H.
Director, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Ms. Taylor:

Please refer to your supplemental new drug applications dated February 3, 1997 (S-002), February 14, 1997 (S-003), and June 17, 1997 (S-005), received February 4 and 18, and June 19, 1997, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rezulin™ (troglitazone) Tablets, 200 mg and 400 mg.

We acknowledge receipt of your submissions to S-002 and S-003 dated February 14 and 20, March 14, April 3, 14, 16, and 29, May 5, 14, 16, 23, and 28, June 4, 11, and 20, and July 2 and 29, 1997. We also acknowledge the submission to S-005 dated July 8, 1997. The User Fee goal dates for these application are February 4, 1998 (S-002), February 18, 1998 (S-003), and December 19, 1997 (S-005), respectively.

These supplemental applications provide for:

1. S-002 adds the use of Rezulin™ in combination with sulfonylureas in the treatment of type II diabetes (new indication);

2. S-003 adds the use of Rezulin™ as monotherapy in type II diabetes (new indication);

3. S-005 adds a new 300 mg tablet dosage form (new strength).

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submissions dated July 8, 1997 (container labels for 300 mg tablets in bottles of 60 and 120 and blister packages) and July 29, 1997 (package insert.) Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on July 8 (300 mg container and blister labels) and July 29 (package insert), 1997.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days

after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved supplemental NDA 20-720/S-002, S-003, S-005." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

A draft protocol, including the study length and number of patients to be studied, will be submitted to the FDA for approval within three months of the approval of this NDA.

The protocol, data, and final report should be submitted to your IND for this product and a copy of each cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of the commitment. The status summary should include the number of patients entered, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

SS 8-4-97
Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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cc:
Original NDAs 20-720
HFD-510/Div. files
HFD-510/CSO/MJohnston
HFD-510/RMisbin/AFleming/XYsern/SMoore
HFD-870/HAhn/MFossler
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

Drafted by: Mjohnston/File: wpfiles\n20720\S2&3ap
Initialed by: SEE ROUTING SHEET ATTACHED
final: MJohnston

APPROVAL (AP) WITH PHASE 4 COMMITTMENTS (TO SUPPLEMENT 002 & 003)

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Clearance Sheet is for Supplements 002, 003, and 005 to NDA 20-720 (Parke-Davis, Rezulin Tablets, 200 mg and 400 mg) and NDA 20-719 (Sankyo U.S.A, Prelay Tablets, 200 mg and 400 mg) and now 300mg

Name	Title	Signature	Date
R. Misbin, M.D.	Clinical Reviewer		7/30/97
G. Fleming M.D.	Clinical Tm. Ldr		7/30/97
H.Rhee, Ph.D.	Pharmacology Rev.		7/29/97
R. Steigerwalt, Ph.D.	Pharm. Tm. Ldr.	Ronald W Steigerwalt	7/29/97
X.Ysern, Ph.D.	Chemistry	Xavier Ysern	29 JUL 1997
S. Moore, Ph.D.	Chemistry Tm Ldr	Stephen K. Moore	7/29/97
B. Taneja, Ph.D.	Statistician	B K Taneja	7/30/97
D. Marticello, Ph.D.	Biometric Tm Ldr	Dan Marticello	7/31/97
G. Fleming M.D.	Clinical Tm. Ldr	See Above	
M. Askine	DDMAC	Mark W. Askine	7/29/97
E. Galliers	Supervisory CSO	Ellis Galliers	8/1/97
S. Sobel, M.D.	Director. DMEDP		8/4/97
M. Fossler	Biopharm Reviewer		7/31/97
H. Ahn	Biopharm Tm. Ldr.		7/31/97

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FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA #20-720 and NDA #20-719

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Rezulin™ and Prelay™
- Active Ingredient(s): Troglitazone
- Strength(s): 200 and 400 mg
- Dosage Form: Tablets

A. U.S. Patent Number: 4,572,912

Expiration Date: August 28, 2004

Type of Patent: Compound per se and Formulation

Assignee: Sankyo Co. Ltd.

U.S. Agent: Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48105

B. U.S. Patent Number: 5,104,888

Expiration Date: August 28, 2004

Type of Patent: Compound and Formulation

Assignee: Sankyo Co. Ltd.

U.S. Agent: Warner-Lambert Company

C. U.S. Patent Number: 5,457,109

Expiration Date: September 15, 2013

Type of Patent: Method of Use

Assignee: Warner-Lambert Company

D. U.S. Patent Number: 5,478,852

Expiration Date: September 15, 2013

Type of Patent: Method of Use

Assignee: Sankyo Co. Ltd.

U.S. Agent: Warner-Lambert Company

E. U.S. Patent Number: 5,602,133

Expiration Date: September 15, 2013

Type of Patent: Method of Use

Assignee: Warner-Lambert Company

The undersigned declares that the above U.S. Patent Nos. 4,572,912 and 5,104,888 cover the formulation of Rezulin™ and Prelay™ (troglitazone), and Patent Nos. 5,457,109, 5,478,852 and 5,602,133 cover the method of using Rezulin™ and Prelay™ (troglitazone) as approved in NDA 20-720 and NDA 20-719, respectively.

Charles W. Ashbrook

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EXCLUSIVITY SUMMARY for NDA # 20-720 SUPPL # 002 & 003

Trade Name Rezulin™ Generic Name troglitazone 200 mg and 400 mg tablets

Applicant Name Warner-Lambert Inc. HFD- 510 Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /__/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES / X / NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   d) Did the applicant request exclusivity? YES /_X_/ NO /___/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

   Three (3) Years

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #_____ _____

NDA #_____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no." state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 6:**

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 991-032

Investigation #2, Study # 991-055

Investigation #3, Study # _____

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ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1_, Study # 991-032

Investigation #2_, Study # 991-055

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /_X_/ NO /___/ Explain:_____

Investigation #2

IND # _____ YES /_X_/ NO /___/ Explain:_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____

Michael F. Johnston, R.Ph. 6-30-97
Signature Date
Title: Project Manager / Consumer Safety Officer

Solomon Sobel M.D. 8/4/97
Signature of Division Director Date

cc: Original NDA
Division File
HFD-85 Mary Ann Holovac (original) - copy in action package

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ON ORIGINAL

ITEM 13.
MARKET EXCLUSIVITY INFORMATION AND
CERTIFICATION FOR GENERIC DRUG ENFORCEMENT ACT

Item 13.1.
Request and Justification for 3-Year Marketing Exclusivity

THIS WAY

ITEM 13.1.
Request and Justification for 3-Year Marketing Exclusivity

Warner-Lambert requests 3 years of market exclusivity for Rezulin™ (troglitazone) tablets for treatment of type II diabetes. The active ingredient in Rezulin is troglitazone. Troglitazone has not been previously approved for the indication being sought in this supplement. Within the meaning of FDA's proposed regulations implementing the Drug Price Competition and Patent Term Restoration Act of 1984, Rezulin is entitled to 3 years of exclusivity pursuant to those regulations, the statute, and the case law.

Troglitazone qualifies for 3 years of market exclusivity pursuant to 21 USC §355(j)(4)(D)(iii) and (c)(3)(D)(iii).

1. We have searched the scientific literature and lists of approved drug applications. To the best of our knowledge, troglitazone, as monotherapy or in combination with oral hypoglycemic agents for patients with type II diabetes, for which approval is sought in this application, has never been approved in another drug product in the US either as a single entity or as part of a combination product.

2a. Clinical investigations, other than bioavailability or bioequivalence studies, were submitted to support this application. Warner-Lambert Company certifies that, to the best of applicant's knowledge, these clinical studies have not formed part of the basis of a finding of substantial evidence of effectiveness for a previously approved new drug application.

b. The new clinical investigations can be found in Item 8 of the application, SNDA No. 20-720-002, filed concurrently herewith.

3a. Attached is a list of all published studies and publicly available reports of clinical investigations known to the applicant that are relevant to support the application.

b. Warner-Lambert Company certifies that applicant has thoroughly searched the scientific literature and that the list of published studies and publicly available reports is complete and accurate.

c. Warner-Lambert Company certifies that, in applicant's opinion, the present application could not have been approved without the new clinical investigations. The published studies noted in 3.a above are not sufficient to support the approval of the application.

4. Warner-Lambert Company is the sponsor named in the Form FDA 1571 for under which the clinical investigations identified in 2 above was performed.

Troglitazone Bibliography

1.AKANUMA Y, KOSAKA K, TOYODA T, KUZUYA T, SHIGETA Y, KANEKO T, SHICHIRI M. CLINICAL EVALUATION OF A NEW ORAL HYPOGLYCEMIC AGENT CS-045 IN COMBINATION WITH INSULIN. DIABETOLOGIA 39 (SUPPL 1) : A232 (ABSTR 881), AUG 1996.

2. BERKOWITZ K, PETERS R, KJOS S, DUNN M, XIANG A, GOICO J, MARROQUIN A, AZEN S, BUCHANAN T. EFFECTS OF TROGLITAZONE ON INSULIN SENSITIVITY AND B-CELL FUNCTION IN WOMEN WITH PRIOR GESTATIONAL DIABETES. DIABETES 45 (SUPPL 2) : 57A (ABSTR 206), MAY 1996.

3. BERKOWITZ K, PETERS R, KJOS S, GOICO J, MARROQUIN A, DUNN M, AZEN S, BUCHANAN T. EFFECT OF TROGLITAZONE ON INSULIN SENSITIVITY AND SECRETION IN WOMEN WITH PRIOR GESTATIONAL DIABETES. J INVESTIG MED 44 : 112A, JAN 1996.

4.BERKOWITZ R, PETERS R, KJOS SL, GOICO J, MARROQUIN A, DUNN ME, XIANG A, AZEN S, BUCHANAN TA. EFFECT OF TROGLITAZONE ON INSULIN SENSITIVITY AND PANCREATIC BETA-CELL FUNCTION IN WOMEN AT HIGH RISK FOR NIDDM. DIABETES 45 : 1572-9, NOV 1996.

5.BISCHOFF H, LEBOVITZ HE. ORAL ANTIDIABETIC DRUGS IN RESEARCH AND DEVELOPMENT. HANDB EXP PHARMACOL 119 : 651-96, 1996.

6.BLOOMGARDEN ZT. NEW AND TRADITIONAL TREATMENT OF GLYCEMIA IN NIDDM. DIABETES CARE 19 : 295-9, MAR 1996.

7. COMINACINI L, GARBIN U, FRATTA PASINI A, CAMPAGNOLA M, YOUNG MMR, CAPRIATI A. TROGLITAZONE INCREASES THE RESISTANCE OF LDL TO OXIDATION IN HEALTHY VOLUNTEERS. DIABETOLOGIA 39 (SUPPL 1) : A233 (ABSTR 885), AUG 1996.

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10.DUNAIF A, WHITCOMB R. TROGLITAZONE (TRO) IMPROVES INSULIN SENSITIVITY AND AMELIORATES REPRODUCTIVE ABNORMALITIES IN THE POLYCYSTIC OVARY SYNDROME (PCOS). DIABETES 45 (SUPPL 2) : 19A (ABSTR 61), MAY 1996.

11.ECKLAND DJA, WILLIAMS ZV, FOOT EA. TROGLITAZONE IMPROVES GLYCAEMIA BUT DOES NOT INCREASE THE RISK OF HYPOGLYCAEMIA FOLLOWING ALCOHOL IN DIET-TREATED NIDDM SUBJECTS. DIABETOLOGIA 39 (SUPPL 1) : A233 (ABSTR 883), AUG 1996.

12.FOOT EA, WILLIAMS ZV, MOHAMED-ALI V, YUDKIN JS, ECKLAND DJA. TROGLITAZONE BUT NOT GLIBENCLAMIDE REDUCES PROINSULIN-LIKE MOLECULES, RISK FACTORS FOR CARDIOVASCULAR DISEASE, IN NIDDM PATIENTS. DIABETOLOGIA 39 (SUPPL 1) : A69 (ABSTR 256), AUG 1996.

13.HENRY RR. EFFECTS OF TROGLITAZONE ON INSULIN SENSITIVITY. DIABET MED 13 : S148-S150, SEP 1996

14.HULIN B, MCCARTHY PA, GIBBS EM. THE GLITAZONE FAMILY OF ANTIDIABETIC AGENTS. CURR PHARM DES 2 : 85-102, FEB 1996

15.IWAMOTO Y, KOSAKA K, KUZUYA T, AKANUMA Y, SHIGETA Y, KANEKO T. EFFECTS OF TROGLITAZONE. A NEW HYPOGLYCEMIC AGENT IN PATIENTS WITH NIDDM POORLY CONTROLLED BY DIET THERAPY. DIABETES CARE 19 : 151-6, FEB 1996.

16.IWAMOTO Y, KOSAKA K, KUZUYA T, AKANUMA Y, SHIGETA Y, KANEKO T. EFFECT OF COMBINATION THERAPY OF TROGLITAZONE AND SULPHONYLUREAS IN PATIENTS WITH TYPE 2 DIABETES WHO WERE POORLY CONTROLLED BY SULPHONYLUREA THERAPY ALONE. DIABETE MED 13 : 365-70, APR 1996.

17.IZUMI T, ENOMOTO S, HOSIYAMA K, SASAHARA K, SHIBUKAWA A, NAKAGAWA T, SUGIYAMA Y. PREDICTION OF THE HUMAN PHARMACOKINETICS OF TROGLITAZONE, A NEW AND EXTENSIVELY METABOLIZED ANTIDIABETIC AGENT, AFTER ORAL ADMINISTRATION, WITH AN ANIMAL SCALE-UP APPROACH. J PHARMACOL EXP THER 277 (3): 1630-41, 1996.

18.KOTCHEN TA. ATTENUATION OF HYPERTENSION BY INSULIN-SENSITIZING AGENTS. HYPERTENSION 28 (2): 219-23, 1996.

19.KUEHNLE HF. NEW THERAPEUTIC AGENTS FOR THE TREATMENT OF NIDDM. EXP CLIN ENDOCRINOL DIABETES 104 (2): 93-101, 1996.

20.KUMAR S, BOULTON AJM, BECK-NIELSEN H, BERTHEZENE F, MUGGEO M, PERSSON B, SPINAS GA, DONOGHUE S, LETTIS S, STEWART-LONG P. TROGLITAZONE, AN INSULIN ACTION ENHANCER, IMPROVES METABOLIC CONTROL IN NIDDM PATIENTS.DIABETOLOGIA 39 : 701-9, JUN 1996.

21.LEVIN K, THYE-RONN P, FOOT E, BECK-NIELSEN H. METABOLIC EFFECTS OF TROGLITAZONE IN NIDDM PATIENTS. DIABETES 45 (SUPPL 2) : 18A (ABSTR 57), MAY 1996.

22.NOLAN JJ, OLEFSKY JM, NYCE MR, CONSIDINE RV, CARO JF. EFFECT OF TROGLITAZONE ON LEPTIN PRODUCTION: STUDIES IN VITRO AND IN HUMAN SUBJECTS. DIABETES 45 : 1276-8, SEP 1996.

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Item 13.2.
Certification of Generic Drug Enforcement Act of 1992

Item 13.2.

Certification of Generic Drug Enforcement Act of 1992

Warner-Lambert Company certifies that it is not debarred. Warner-Lambert Company did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

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commercial

information

NDA 20-720/S-002 & S-003
Rezulin™ 200 mg & 400 mg tablets

These NDA Supplements will be approved at the Division Director Level - No Division Director's Memo will be done.

Group Leader's Summary Comments

Rezulin ™ (troglitazone)

Supplements to NDA 20-719 and 20-720

September 30, 1997

Background

The sponsor has supplemented its approved NDA with data in support of expanding the indications for troglitazone as monotherapy in all type 2 patients and for use of this drug in combination with sulfonylureas in type 2 patients inadequately controlled on SU therapy alone. Our understanding of troglitazone's safety profile is largely based on previously reviewed studies. The submitted studies are mainly intended to demonstrate efficacy for the indications being sought. Dr. Misbin has expertly reviewed these studies in depth and led the interactive crafting of appropriate labeling. I will emphasize a few of the conclusions and recommendations that he has already made.

DISCUSSION OF ISSUES

This summary highlights what I consider to be the important issues related to the evaluation of troglitazone for the proposed indication.

1. Troglitazone is marginally effective as monotherapy.

As pointed out in the medical officer's review (MOR) and best shown in figure 3 on page 8a of the MOR, troglitazone has minimal efficacy when used as monotherapy in a general population of type 2 diabetics over a 6 month period. With this dose response design, a roughly dose proportional improvement in FBG at 6 months was observed from 200-600 mg with respect to week 0 values. The lowest dose, 100 mg, did not differ with placebo. However, week 0 values were actually significantly higher than those that were observed before patients' SU therapy was discontinued. Thus, the 400 and 600 mg doses were barely able to equal the FBG levels seen while patients were on SU therapy. Even when compared to the week 0 baseline, only the 400 and 600 mg doses resulted in statistically significant improvements in HbA1c.

2. The recommended starting dose of 400 mg is not supported by the results from the pivotal study.

In the pivotal study, the 400 mg dose treatment HbA1c effect (-.06) was actually less than that seen with the 200 mg dose (-.65). Thus, that study alone does not provide a strong basis for recommending any less than a 600 mg starting dose. In all probability, the minimal response seen with 400 mg occurred by chance in this relatively small study. FBG levels were comparable for the 400 and 600 mg groups. Moreover, the sponsor was able to respond to Dr. Misbin's request that other data supporting a lower dose be submitted. Studies 057 and 031, though relatively small and or shorter duration, demonstrated a response at 200 mg. I believe, therefore, that we have ample evidence to support a starting dose of 400 mg. This recommendation will avoid an excessive drug exposure for the subgroup of more sensitive patients.

3. Combination therapy of troglitazone and SU is supported only by one study

In the single pirvotal study of SU-troglitazone combintio therapy, true synergy of the combination was clearly demonstrated. This one year study is more than large enough to suffice as a basis for approving this new indication given the prior experience reviewed in the original NDA.

4. Troglitzone continues to carry concerns about fluid distribution among body compartments and cardiotoxicity.

Troglitazone is a member of a class of compounds that have been associated with cardiac toxicity. Troglitazone itself was found in various animal studies to be associated with increased heart weights primarily due to fluid accumulation within heart muscle, and with some small histologic effects as well. In short term studies, this effect was shown to be reversible in mice. A one year study of monkeys was negative for functional cardiovascular changes at 3 to 5 times the expected human exposure at the 400 mg dose.

In study 032, 15 patients (4.6%) on troglitazone vs. 0 in the placebo group developed peripheral edema. One patient in study 055 developed pulmonary edema. This further substantiates a concern than troglitazone affects fluid distribution as well as causing fluid retention of a perculiar kind. Levels of atrial naturetic factor (ANF) have been found to be unaffected by troglitazone therapy. This will the drug's slight hypotensive effect suggest that baroceptor function is altered by the drug. Serious clinical consequences of troglitazone have not been definitely tied to these effects on fluid distribution, but it is hard to believe that patients with cardiac, liver, or renal disease would not be adversely affected by the drug.

The 96 week echocardiography study revealed no differences between treatment groups

(troglitazone and glyburide) in terms of carciac toxicity but as our consultant, Dr. Lapicki stated this simply means that "no major harm has occurred." Thus while this study provides some reassurance, the study of more sensitive patients, i.e. those with heart failure, and long term surveillance will be necessary to absolve the drug of this effect. Clearly some concern is warranted about the effects of troglitazone on the heart in humans treated for many years. The labeling now reinforces this point.

Labeling

Dr. Misbin has provided an excellent set of suggested label modifications and these have been entriely incorporated in the final version.

CONCLUSIONS

Troglitazone therapy is very effective when used in combination with SU and for poorly controlled patients on insulin therapy. Troglitzone's value as a monotherapy is marginal, but its mechanism of action is more appealing than that of SUs. Monotherapy therefore may be of value in some patients who are adequately responsive. Significant safety issues identified in the original NDA continue to be a concern, but the labeling adequately reflects these concerns. Studies are in place that will help to resolve these safety issues.

RECOMMENDATIONS

The indications for monotherapy and therapy in combination with sulfonylureas should be approved. The final draft labeling should be adopted.

7/31/97

Alexander Fleming, M.D.

JUL 3 1997

MEDICAL OFFICER'S REVIEW

NEW DRUG APPLICATION 20-720

Supplements for

TROGLITAZONE (REZULIN) for treatment of type 2 diabetes

Monotherapy
Combination with sulfonylureas

Sponsor - PARKE DAVIS

submitted February 3 and 14, 1997

TABLE OF CONTENTS

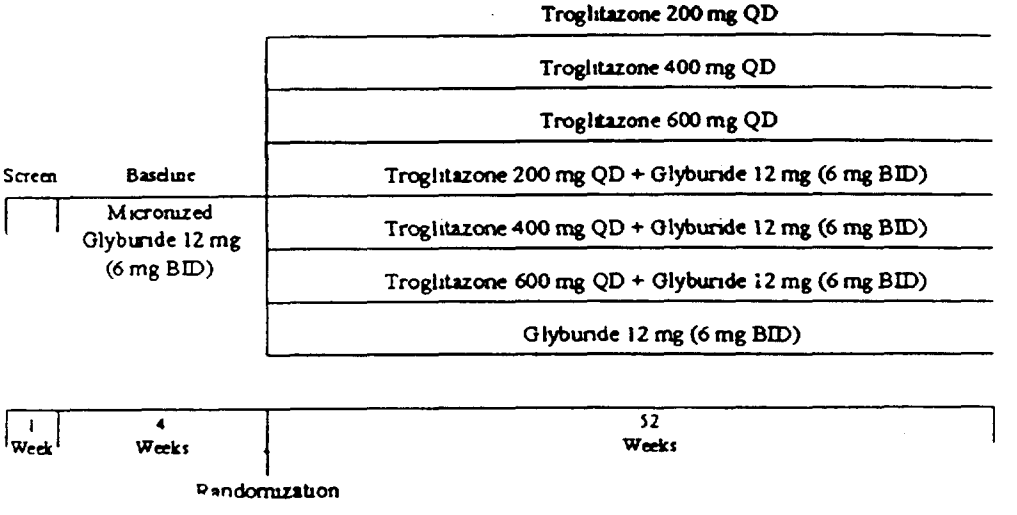
Introduction

NDA 20-720, Troglitazone (Rezulin) for poorly controlled insulin-treated patients with type 2 diabetes was approved January 29, 1997. Supplements for monotherapy and combination therapy with sulfonylureas were submitted on February 14 and 3, respectively. This review focuses on the efficacy and labeling issues raised by the studies submitted in those supplements. Background, mechanism of action, clinical pharmacology, etc. were covered by Dr Fleming in his review of January 17, 1997 and will not be repeated here except where pertinent to the supplement. A review of the safety update submitted by the Sponsor May 23 1997 is also included.

In support of the indication for combination therapy with sulfonylureas, the Sponsor submitted data from a single 12 month double blind placebo controlled study (study 055). In support of the monotherapy indication, the Sponsor submitted data from one six month double blind placebo controlled study (study 032) and a 12 week double blind placebo controlled study (study 031). Data from a 20 week study (study 057) of monotherapy was also submitted but this study had no placebo control. Also relevant to the monotherapy indication is an open label 96 week (study 042) comparison of troglitazone with glyburide. Results of each of these studies are discussed individually.

055 - Troglitazone and troglitazone with glyburide in patients previously treated with maximal dose sulfonylureas with pharmacokinetic studies at some centers

This was a one year study of patients with fasting C-peptide of greater than 1.5 ng/ml and FSG of $\geq$ 140mg and HbA1c $\geq$ 5.9% while on maximal dose sulfonylureas. Patients were stabilized on 6 mg bid of Glynase and then randomized to glynase alone, troglitazone alone 200, 400 mg, or 600 mg, or troglitazone plus glynase. The primary measures of efficacy were changes from baseline of HBA1c and FSG after 52 weeks. Secondary measures of efficacy were serum insulin levels, and various lipid measurements. Meal tolerance studies, pharmacokinetic studies, and echocardiography studies were also performed at some centers. Patients were classified as "responders" if they showed a 1% absolute fall in HbA1c from a baseline. Hypoglycemia was defined as FSG<50 mg/dl verified by laboratory measurement.



The study group was 60% male, mean age 57.5 years with a mean duration of diabetes of 8.4 Years/ They were 76.8% white, with mean body mass index of 32.1. Baseline laboratory measurements were FSG 224 mg/dl, HbA1c 9.6 %, insulin 29 uU/ml, C-peptide 2.8 ng/dl. Mean weight at baseline was 205 lbs. Each study group had about 78 patients entered. As shown in the table, 85% of patients in combined 600 mg troglitazone with glyburide completed the study compared to 58% on glyburide and 44% on 600 mg troglitazone alone. Lack of efficacy was the most common reason for failure to complete the study for patients on troglitazone monotherapy. Only 3.7% of patients on the high dose combination dropped out because of lack of efficacy compared to 25% on Glyburide alone and 44% on 600 mg troglitazone.

Study arm

TABLE 6. Patient Disposition
[Number (%) of Patients]

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg		
Randomized to Treatment	78	81	78	78	76	82	79	552
Withdrawn Prior to End of Treatment								
Lack of Efficacy	43 (55.1)	32 (39.5)	34 (43.6)	11 (14.1)	7 (9.2)	3 (3.7)	20 (25.3)	150 (27.2)
Adverse Event	6 (7.7)	7 (8.6)	6 (7.7)	5 (6.4)	8 (10.5)	5 (6.1)	6 (7.6)	43 (7.8)
Lack of Compliance	3 (3.8)	2 (2.5)	3 (3.8)	0 (0.0)	1 (1.3)	2 (2.4)	1 (1.3)	12 (2.2)
Pregnancy	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	4 (5.1)	3 (3.7)	1 (1.3)	6 (7.7)	6 (7.9)	2 (2.4)	6 (7.6)	28 (5.1)
Total	56 (71.8)	45 (55.6)	44 (56.4)	22 (28.2)	22 (28.9)	12 (14.6)	33 (41.8)	234 (42.4)
Completed Study[a]	22 (28.2)	36 (44.4)	34 (43.6)	56 (71.8)	54 (71.1)	70 (85.4)	46 (58.2)	318 (57.6)

[a] Based on investigator's response on termination case report form

Results:

Both FSG and HbA1c rose after 12 months of treatment in patients on glyburide alone but fell in patients on glyburide plus all three doses of troglitazone. Levels rose in patients on 200 mg troglitazone monotherapy who completed the study but were largely unchanged at 400 mg and 600 mg. These results are shown in the table. When corrected for the rise with glyburide alone, the treatment effect of 600 mg troglitazone when given with glyburide was 2.65% for HbA1c and 79.1 mg/dl of FSG. Smaller but still significant changes were seen at 200 mg. Intermediate value were observed with 400 mg, indicating a clear dose-response relationship in the range 200 - 600 mg per day. A time course of the effect using an intent to treat population is shown in the figure. The maximal troglitazone effect for FSG required about eight weeks. The deterioration which occurred in patients on troglitazone monotherapy occurred during the first four weeks but stabilized thereafter. Among patients who completed the study, all troglitone treatment groups, except 200 mg monotherapy, had significantly improved glycemic control compared to glyburide alone. With respect to HbA1c, the drug effect of 600 mg of troglitazone with glyburide was 2.74%, and 51% of patients achieved a reduction in HbA1c of 1% or more (see table 9).

The efficacy in the ITT population (shown in the figure) is different from that in the completer population shown in the table. This discrepency is due to the high drop-out rate in patients taking troglitazone alone, primarily because of lack of efficacy. As shown in table 6, dropouts due to lack of efficacy were 55%, 40%, and 44% for 200 mg,400mg, 600mg troglitazone respectively compared to 25% with glyburide.

Fasting insulin and C peptide values fell in all troglitazone groups. The fall was greatest in those patients on troglitazone monotherapy, presumably because the glyburide had been discontinued. A small rise in total cholesterol and LDL cholesterol was seen in patients on troglitzone monotherapy and to a lesser extent on combined therapy but there were also small rises in HDL cholesterol There were no changes in Apo A1, Apo B or Lp(a)or VLDL. A 2.6 mmHg in diastolic blood pressure ($p<0.05$) was seen with the 600mg/12 mg combination vs. 12 mg glyburide. Body weight increased in all combination treatment groups. The weight gain in the 600 mg/12 combination was 14.4 pounds vs glyburide alone (see table 14). The change in body appeared to be correlated to changes in glycemic control.

Study 0V-V-

TABLE 9. Primary Parameters at Week 52: Completers

Parameter	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Hemoglobin A_{1c}, %							
Mean Baseline (SD)	9.53 (1.57)	9.07 (1.61)	9.35 (1.77)	9.33 (1.35)	9.60 (1.32)	9.35 (1.53)	9.49 (1.33)
Adjusted Mean Change From Baseline (SE)	0.55 (0.38)	-0.25 (0.29)	-0.26 (0.30)	-0.85 (0.24)	-1.10 (0.24)	-1.96 (0.21)	0.78 (0.27)
Adjusted Mean Difference From Glyburide Monotherapy (SE)	-0.23 (0.46)	-1.03* (0.38)	-1.04* (0.39)	-1.63** (0.35)	-1.88** (0.34)	-2.74** (0.33)	..
95% Confidence Interval[a]	(-1.43 to 0.97)	(-2.02 to -0.04)	(-2.06 to -0.02)	(-2.54 to -0.73)	(-2.77 to -0.99)	(-3.60 to -1.88)	
Fasting Serum Glucose, mg/dL							
N							
Mean Baseline (SD)	217.5 (44.6)	196.8 (42.4)	212.4 (48.9)	221.7 (55.7)	224.6 (43.0)	218.5 (51.1)	214.7 (34.5)
Adjusted Mean Change From Baseline (SE)	13.4 (12.0)	-20.5 (9.4)	-11.7 (9.8)	-34.1 (7.6)	-46.0 (7.7)	-58.1 (6.8)	13.1 (8.6)
Adjusted Mean Difference From Glyburide Monotherapy (SE)	0.3 (14.6)	-33.6* (12.3)	-24.8 (12.6)	-47.2** (11.2)	-59.1** (11.1)	-71.2** (10.6)	..
95% Confidence Interval[a]	(-37.6, 38.2)	(-65.5, -1.8)	(-57.5, 7.8)	(-76.3, -18.1)	(-87.8, -30.4)	(-98.7, -43.7)	

[a] ANCOVA (with treatment and center effects and baseline as covariate).

* $p \leq 0.05$

** $p \leq 0.0001$

RR 720-03526

6a

Study Ovv-

TABLE 8 Change From Baseline at Month 12 in Primary Glycemic Parameters
ITT Population: Study 991-055

Parameter	Troglitazone Monotherapy			Combination Therapy:Troglitazone/Glyburide			Glyburide Monotherapy
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	
Fasting Serum Glucose, mg/dl.							
Mean Baseline	226.3	212.9	230.2	225.7	230.9	220.8	222.2
Adjusted Mean Change From Baseline (SE)	42.4 (7.0)	20.6 (7.0)	11.1 (7.1)	-31.0 (7.0)	-38.0 (7.1)	-56.4 (6.9)	22.7 (6.9)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	19.6 (9.7)	-2.2 (9.7)	-11.6 (9.7)	-53.7** (9.7)	-60.8** (9.7)	-79.1** (9.6)	
95% Confidence Interval[b]	(-5.3, 44.6)	(-27.1, 22.8)	(-36.7, 13.4)	(-78.6, -28.9)	(-85.8, -35.7)	(-103.9, -54.4)	
Hemoglobin A_{1C}, %							
Mean Baseline	9.54	9.44	9.71	9.49	9.72	9.45	9.57
Adjusted Mean Change From Baseline (SE)	1.92 (0.20)	0.85 (0.20)	0.93 (0.20)	-0.70 (0.20)	-0.91 (0.20)	-1.75 (0.20)	0.90 (0.20)
Adjusted Mean Difference From Glyburide Monotherapy (SE)[a]	1.02* (0.28)	-0.05 (0.28)	0.03 (0.28)	-1.60** (0.28)	-1.81** (0.28)	-2.65** (0.28)	--
95% Confidence Interval[b]	(0.31, 1.74)	(-0.76, 0.66)	(-0.69, 0.75)	(-2.31, -0.88)	(-2.53, -1.10)	(-3.36, -1.94)	

[a] ANCOVA with treatment and center effects and baseline as covariate using stepdown test of linear-trend or Bonferroni-Holm adjustment.
[b] 95% confidence intervals based on Dunnett's test.
* $p \leq 0.001$
** $p \leq 0.0001$

28

Study 055

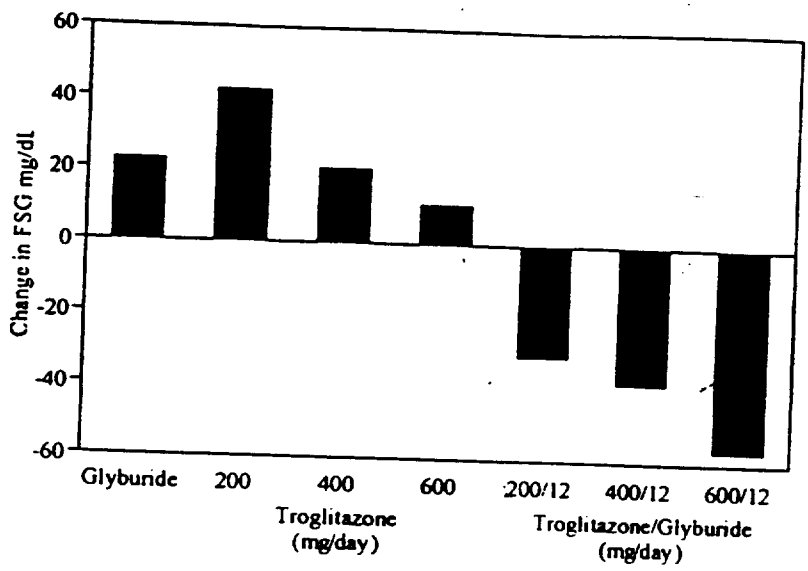


FIGURE 2. Mean Change From Baseline in FSG at Week 52 (ITT)

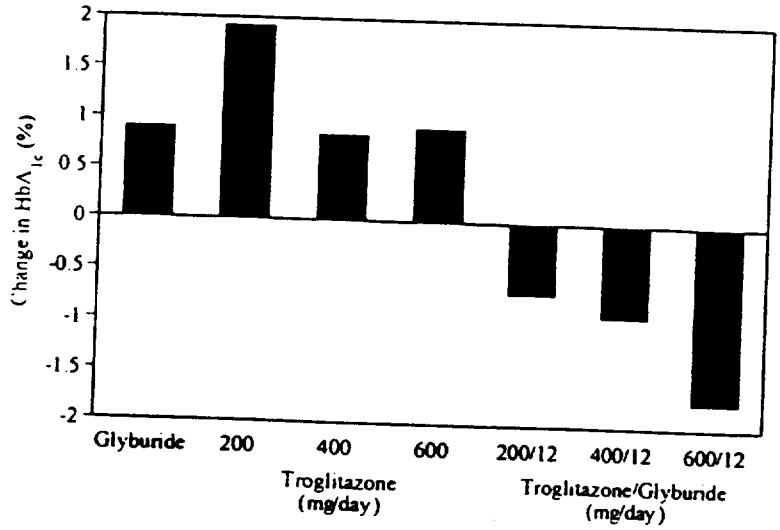


FIGURE 3 Mean Change From Baseline in HbA_{1C} at Week 52 (ITT)

Figure 4 illustrates the mean levels of FSG and HbA_{1C} over time for the ITT population. The majority of improvement in glycemic control (FSG) was observed by the fourth week of therapy.

Study 055

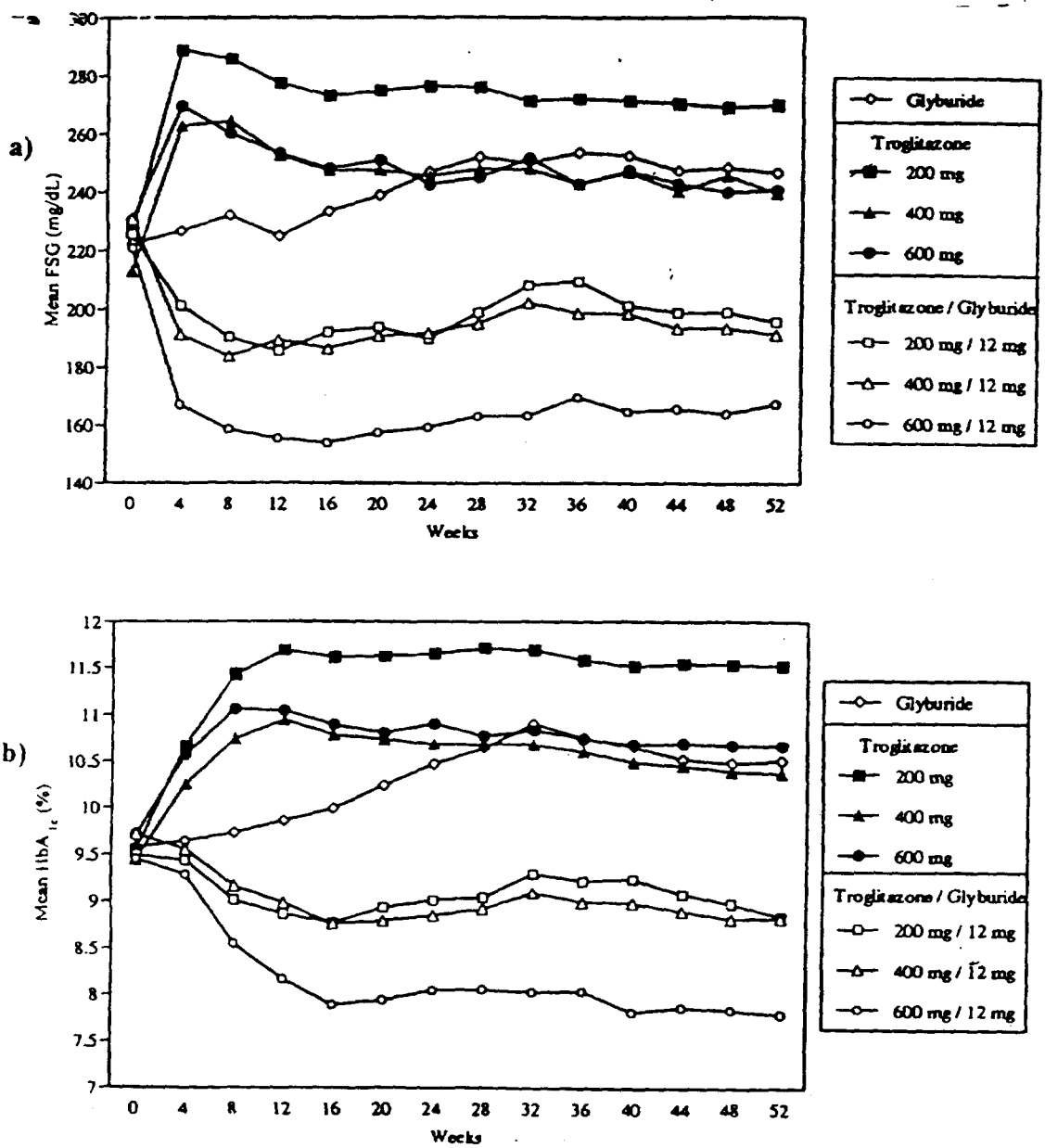


FIGURE 4 Mean Levels of a) FSG and b) HbA_{1C} by Time (ITT)

TABLE 6. Patient Disposition
[Number (%) of Patients]

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg		
Randomized to Treatment	78	81	78	78	76	82	79	552
Withdrawn Prior to End of Treatment								
Lack of Efficacy	43 (55.1)	32 (39.5)	34 (43.6)	11 (14.1)	7 (9.2)	3 (3.7)	20 (25.3)	150 (27.2)
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Lack of Compliance	3 (3.8)	2 (2.5)	3 (3.8)	0 (0.0)	1 (1.3)	2 (2.4)	1 (1.3)	12 (2.2)
Pregnancy	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	4 (5.1)	3 (3.7)	1 (1.3)	6 (7.7)	6 (7.9)	2 (2.4)	6 (7.6)	28 (5.1)
Total	56 (71.8)	45 (55.6)	44 (56.4)	22 (28.2)	22 (28.9)	12 (14.6)	33 (41.8)	234 (42.4)
Completed Study[a]	22 (28.2)	36 (44.4)	34 (43.6)	56 (71.8)	54 (71.1)	70 (85.4)	46 (58.2)	318 (57.6)

[a] Based on investigator's response on termination case report form

TABLE 14 Mean Change From Baseline in Body Weight at Month 12: ITT

	Troglitazone Monotherapy (mg)			Troglitazone/Glyburide (mg) Combination Therapy			Glyburide
	200 N = 79	400 N = 78	600 N = 76	200/12 N = 77	400/12 N = 75	600/12 N = 79	N = 79
Mean Baseline (SD)	201.7 (42.0)	216.6 (54.8)	207.1 (46.1)	202.5 (35.8)	200.6 (42.4)	196.2 (43.2)	196.2 (43)
Adjusted Mean Change (SE)	-6.9 (1.2)	-3.9 (1.2)	-0.8 (1.2)	5.8 (1.2)	7.7 (1.2)	13.1 (1.2)	-1.3 (1.2)
Difference From Glyburide (SE)	-5.6* (1.6)	-2.6 (1.6)	0.5 (1.6)	7.1** (1.6)	9.0** (1.6)	14.4** (1.6)	.. ..

* $p \leq 0.05$.
** $p \leq 0.0001$

TABLE 11. Responders at Week 52: ITT

Responders as Defined by:	Troglitazone Monotherapy (mg)			Troglitazone/Glyburide (mg) Combination Therapy			Glyburide
	200 N = 78	400 N = 78	600 N = 76	200/12 N = 78	400/12 N = 76	600/12 N = 80	
≥30 mg/dL Reduction in FSG[a]							
Responders, N (%)	11 (14)	20 (26)	18 (24)	37*(47)	47* (62)	53* (66)	10 (13)
≥1% Reduction in HbA_{1c}[a]							
Responders, N (%)	3 (4)	13 (17)	8 (11)	29*(37)	39* (51)	51* (64)	4 (5)

* $p \leq 0.001$, significantly different from glyburide (based on step-down CMH tests)
[a] From baseline

Safety:

There was one death on glyburide due to acute pulmonary edema and one death on 600 mg troglitazone due to acute myocardial infarction. There were five patients who reported hypoglycemia, three of which were in the 600mg/12 mg group. No patient discontinued treatment because of hypoglycemia, but one patient had the dose of glyburide reduced. The adverse events and laboratory abnormalities found in this study are similar to other studies of troglitazone and will be discussed in a later section. These include diarrhea, fall in hematocrit, rise in LDH and significant but reversible rise in liver transaminases. There were no significant differences between the treatment groups with respect to cardiac parameters (see table 20)

Conclusion:

This study shows that the combination of troglitazone with glyburide had greater efficacy than could be achieved by maximal doses of either agent alone. The study also shows that patients on glyburide who are switched to troglitazone can expect to experience a deterioration in glycemic control. Therefore troglitazone should be ADDED to a sulfonylurea but should not generally be used IN PLACE of a sulfonylurea. Improvement in glycemic control with troglitazone appears to be associated with a rise in body weight.

Study 017

TABLE 20 Mean Cardiac Parameters in Patient Subset at Month 12: ITT

Parameter	Troglitazone Monotherapy			Troglitazone/Glyburide Combination Therapy			Glyburide
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg	Control 12 mg
Left Ventricular Mass Index, gr/m²							
N	9	6	6	8	7	11	10
Baseline (SD)	68.8 (11.1)	63.8 (7.3)	69.5 (14.6)	73.1 (16.1)	76.6 (15.2)	65.0 (11.6)	72.9 (19.4)
Change from Baseline Month 12 (SD)	-2.6 (7.6)	-0.5 (3.0)	-5.2 (3.2)	-1.5 (6.9)	0.2 (6.7)	-2.8 (6.9)	0.4 (6.0)
Cardiac Index, L/min/m²							
N	9	6	6	8	7	11	10
Baseline (SD)	2.47 (0.5)	2.15 (0.4)	2.35 (0.3)	2.27 (0.5)	2.36 (0.4)	2.28 (0.5)	2.16 (0.5)
Change from Baseline Month 12 (SD)	-0.09 (0.5)	0 (0.3)	0.19 (0.6)	0.06 (0.5)	0.37 (0.6)	0.03 (0.5)	0.01 (0.4)
Stroke Volume Index, mL/m²							
N	9	6	6	8	7	11	10
Baseline (SD)	35.3 (8.5)	31.9 (6.0)	30.8 (2.6)	32.3 (7.0)	31.3 (2.9)	32.2 (6.6)	28.5 (6.1)
Change from Baseline Month 12 (SD)	-2.9 (5.4)	-2.2 (5.1)	3.4 (4.8)	1.3 (4.9)	5.4 (7.7)	-0.1 (4.0)	1.1 (4.9)
Peripheral Resistance, dd							
N	8	6	6	7	7	11	10
Baseline (SD)	40.4 (6.5)	46.7 (10.2)	39.7 (7.8)	45.3 (10.7)	42.2 (9.3)	43.3 (8.6)	44.7 (11.5)
Change from Baseline Month 12 (SD)	-1.3 (5.6)	-2.3 (7.7)	-2.4 (8.4)	-3.8 (12.2)	-8.3 (10.7)	0.1 (8.7)	-0.4 (11.2)

032 - Troglitazone as Monotherapy in NIDDM

This was a six month parallel trial of troglitazone at 100, 200, 400,and 600 mg/d versus placebo in patients with NIDDM whose HbAlc was greater than 6.5 FSG >140 mg/dl and C peptide of 1.5 ng/ml or greater. There was a two-week washout period from prior therapy (no greater than ½ maximal dose SFU), followed by six months of active treatment. Each treatment group had about 80 patients. There was a mean age of 54 years, 59% male, 74.4% white, a mean body mass index of 32.5, and mean duration of diabetes of 5.3 years.

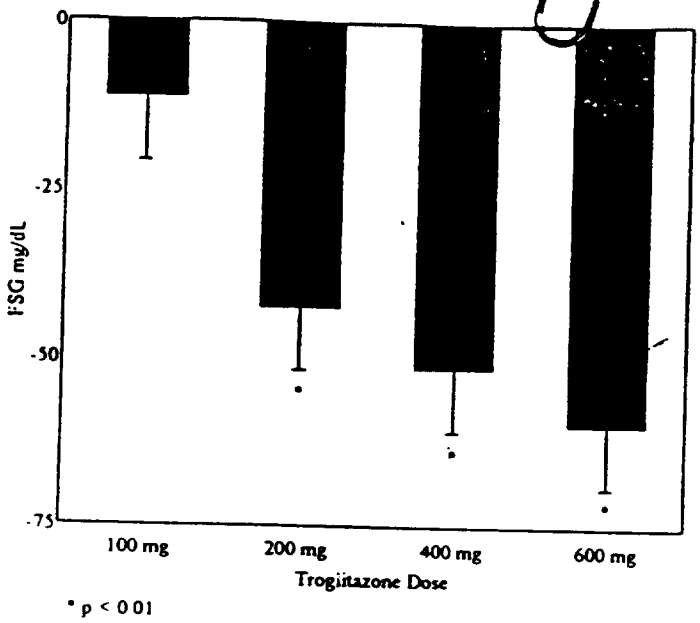
Results:

As shown in figure 2 &3, troglitazone in doses of 200-600 mg/day caused a statistically significant reduction in FSG versus placebo. A reduction vs placebo in HbAlc was also observed but was not statistically significant at 200 mg/day. However as shown in tables 8&9, the troglitazone's effect relative to placebo was largely related to preventing the deterioration in glycemic control in the placebo patients. From the time course shown in figure 3, it is clear that glucose rises during the two week wash-out period when previous SFU is withdrawn. This elevation in glucose relative to previous therapy persists after 6 months in patients on placebo, but is ameliorated for patients on 400 and 600 mg troglitiazone. With respect to HbAlc, the rise of 1.5% in placebo patients compared to a rise of only 0.4% on 600 mg troglitazone gives a significant drug effect of -1.1 % units even though glycemia was not actually improved.

The deterioration in glycemic control early in the study can largely be accounted for by discontinuation of previous medication in patients on sulfonylureas (SFU). As shown in the table, more than 75% of patients in this study had been on a SFU (86 on diet alone and 306 on SFU). Mean FSG went up 41.4 mg/dl during the two-week washout period in the SFU patients vs 3 mg/dl in previously untreated patients.

28
std 032

a)



b)

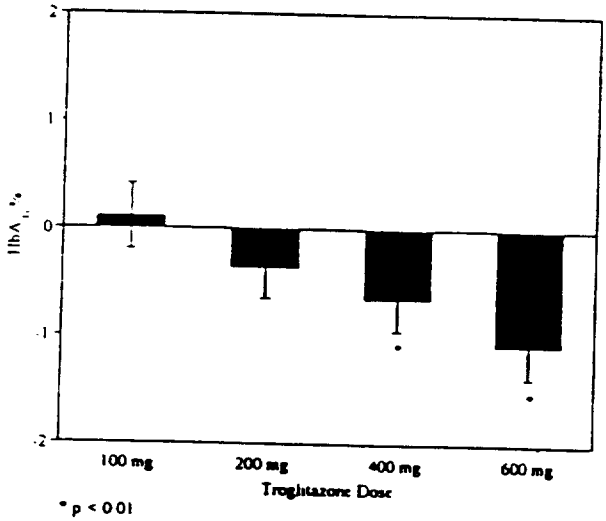


FIGURE 2 Adjusted Mean Difference From Placebo in a) FSG and b) HbA_{1C} at Month 6 (ITT)

20
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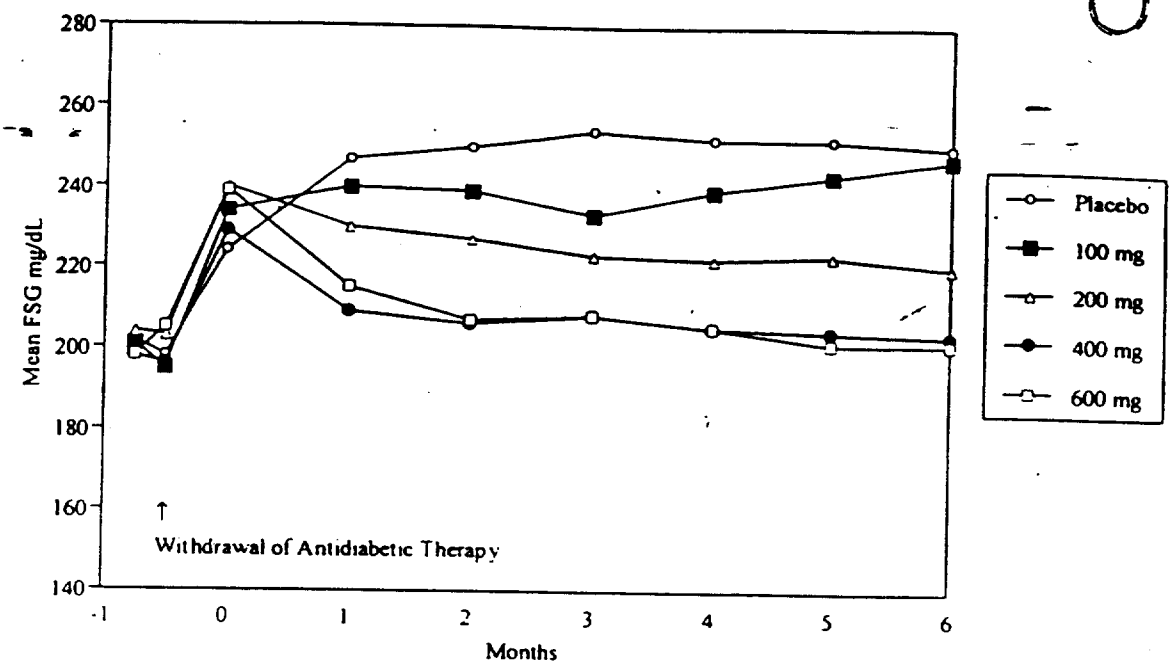


FIGURE 3 Mean FSG by Time, Including Screening and Baseline Values (ITT)

TABLE 8 Primary Efficacy Parameters at Month 6: ITT (LOCF)

Parameter	Placebo	Troglitazone (mg)			
		100	200	400	600
HbA_{1C}, %					
N	78	78	81	76	79
Mean Baseline (SD)	8.7 (1.7)	8.6 (1.7)	8.6 (1.7)	8.6 (1.8)	8.9 (1.7)
Adjusted Mean Change From Baseline (SE)	1.5 (0.2)	1.6 (0.2)	1.1 (0.2)	0.8 (0.2)	0.4 (0.2)
Difference From Placebo	--	0.1	-0.4	-0.7*	-1.1*
(CI)		(-0.6, 0.8)	(-1.1, 0.4)	(-1.4, 0.1)	(-1.8, -0.4)
Fasting Serum Glucose, mg/dL					
N	79	77	81	76	79
Mean Baseline (SD)	224 (65)	234 (62)	240 (70)	229 (74)	240 (68)
Adjusted Mean Change From Baseline (SE)	24 (7)	13 (7)	-19 (7)	-27 (7)	36 (7)
Difference From Placebo	--	-11	-42*	-51*	60*
(CI)		(-35, 12)	(-65, -20)	(-75, -28)	(-83, -37)

CI = Confidence interval (via Dunnett's test)

* $p \leq 0.01$ (based on step-down for trend test within ANCOVA)

gb

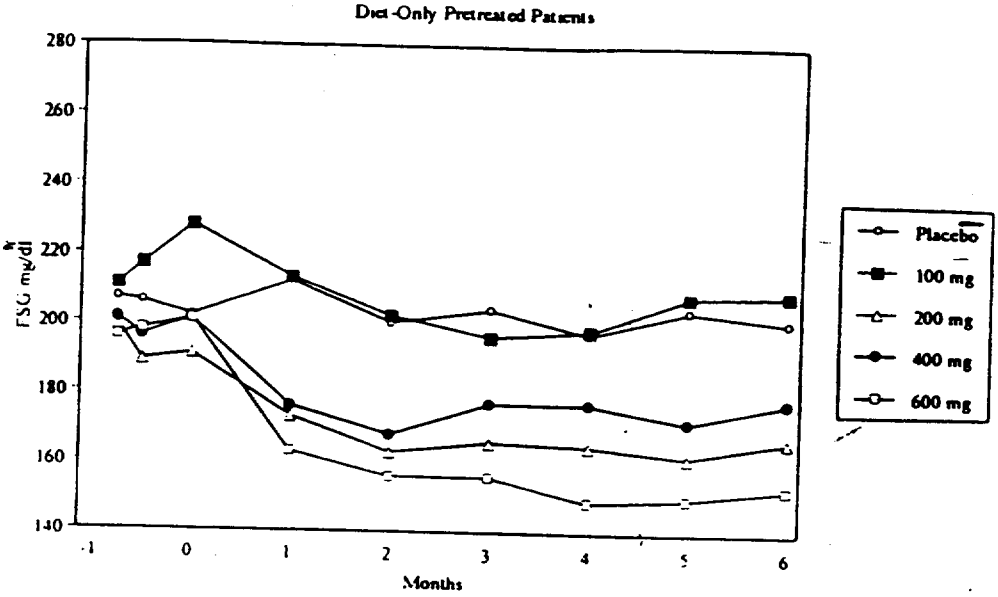
TABLE 9. Change in Glycemic Parameters From Screening (Week -2) to Baseline (Week 0): ITT (Diet Only Prestudy Therapy and Oral Agent Prestudy Therapy) 032

Parameter	Prestudy Therapy		
	Diet Only Therapy		Oral Agent Therapy
Hemoglobin A_{1c}(%)			
N	86		306
Mean at Screening[a] (SD)	8.6 (2.0)		8.4 (1.6)
Adjusted Mean Change From Screening to Baseline (SE)	0.06 (0.07)		0.31 (0.04)
95% CI	(-0.07, 0.19)		(0.24, 0.38)
p-Value for Difference		<0.01*	
Fasting Serum Glucose (mg dL)			
N	87		305
Mean at Screening[a] (SD)	201.2 (56.4)		200.3 (57.1)
Adjusted Mean Change From Screening to Baseline (SE)	3.0 (4.6)		41.4 (2.5)
95% CI	(-6.1, 12.1)		(36.5, 46.2)
p-Value for Difference		<0.01*	
Total Insulin (IU/mL)			
N	87		305
Mean at Screening[a] (SD)	34.6 (21.8)		31.0 (18.2)
Adjusted Mean Change From Screening to Baseline (SE)	-3.5 (1.2)		-5.9 (0.6)
95% CI	(-5.8, -1.2)		(-7.1, -4.6)
p-Value for Difference		0.08	
C-Peptide (ng/mL)			
N	87		306
Mean at Screening[a] (SD)	2.9 (1.2)		2.8 (1.1)
Adjusted Mean Change From Screening to Baseline (SE)	-0.02 (0.09)		-0.30 (0.05)
95% CI	(-0.20, 0.17)		(-0.40, -0.21)
p-Value for Difference		<0.01*	

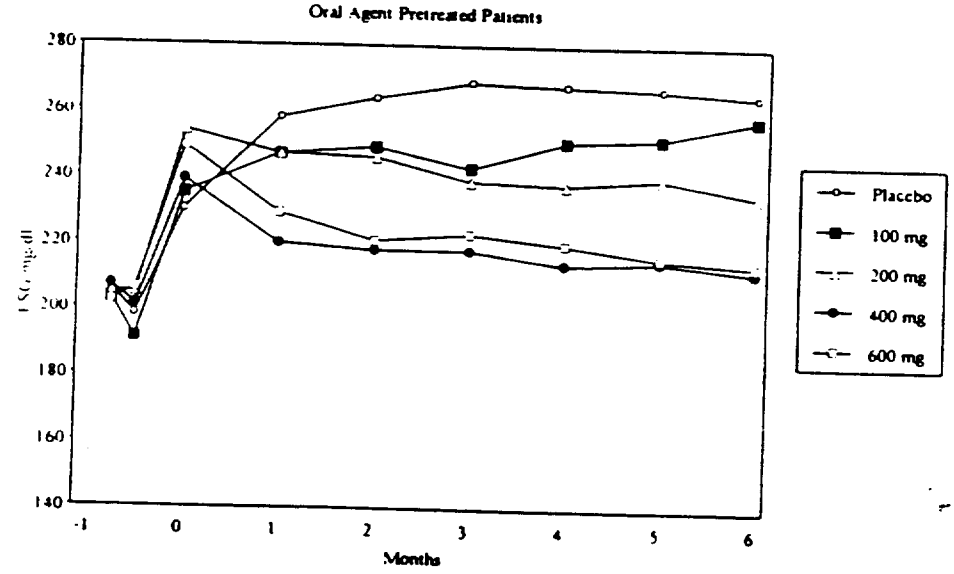
* Statistically significant (<0.05)
[a] Week -2

The next two figures show the time course of the troglitazone effect in patients who were previously on SFU vs those who were on diet alone. With respect to FSG, all groups of patients previously on SFU showed deterioration early in the study. After six months of treatment, patients on 400mg or 600 mg troglitazone were nearly (but not completely) back to their pre-washout levels. For diet only patients, however, a substantial reduction in FSG was observed by two months and maintained until the end of the six-month study. With respect to HbAlc, deterioration was observed in all groups of SFU patients. Even despite 600 mg troglitazone, a 1.0 % unit rise was observed from prewashout levels. Among diet-only patients, 600 mg troglitazone resulted in nearly a 1.0 % unit fall in HbAlc from pre-washout levels.

a)



b)

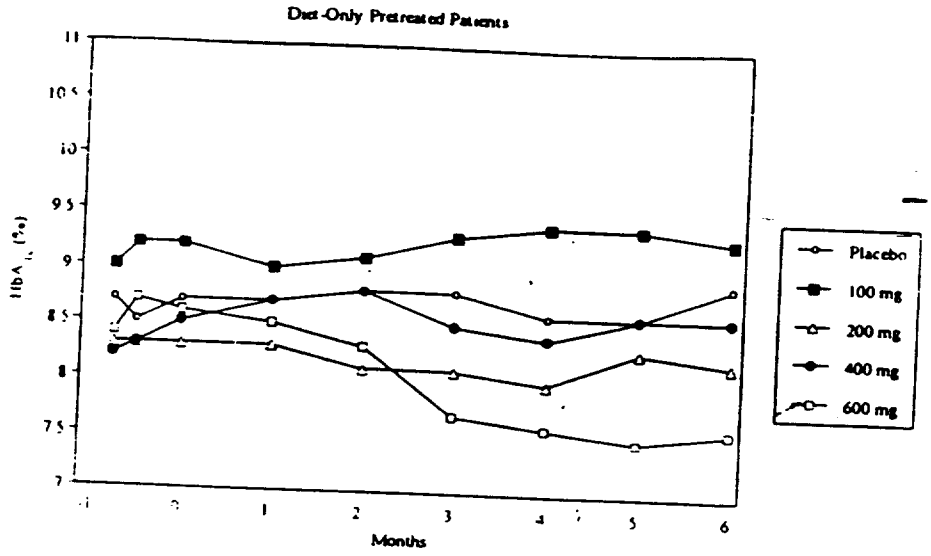


032

FIGURE 4 Mean FSG by Time and Prestudy Therapy

a) Prestudy therapy Diet only, b) Prestudy therapy Oral antidiabetics

a)



b)

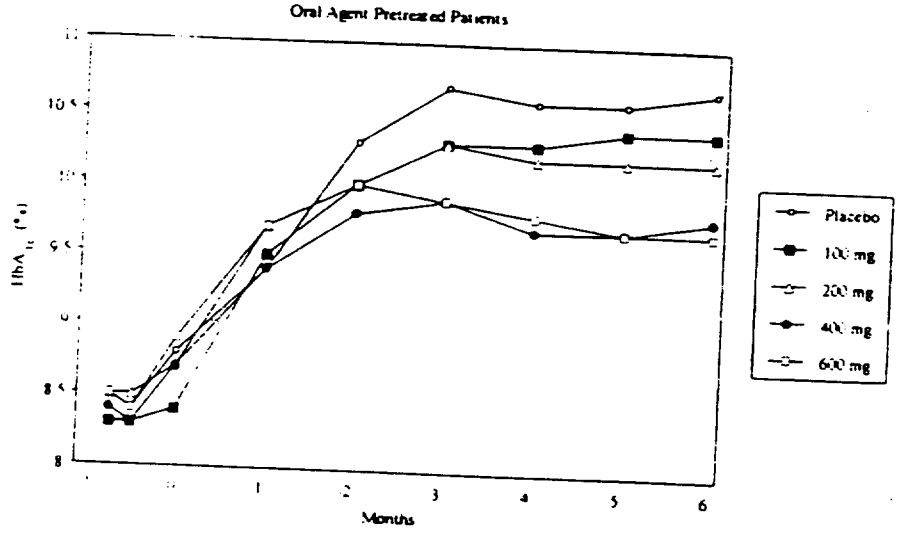


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FIGURE 5 Mean HbA_{1c} by Time and Prestudy Therapy

a) Prestudy therapy Diet only b) Prestudy therapy Oral antidiabetics

The results after six months are shown in the table. Although a clinically significant fall HbA1c and FSG was observed at 600 mg troglitazone, it is disappointing that these results are based on only 15 patients. For patients previously on SFU, it is clear that troglitazone was better than placebo, but that troglitazone never achieved the level of glycemic control observed with previous therapy. These results show that sulfonylureas should not be discontinued in patients treated with troglitazone. Troglitazone monotherapy in previously untreated patients is probably effective but the data base is very small. The Sponsor has put forward a "responder analysis" in the following table. Based on a 1% reduction in HbA1c, and a 30 mg/dl reduction in FSG they find a 19% and 56% response rate respectively in patients previously on SFU. However, this analysis is based on change from baseline, after the deterioration in glycemic control resulting from the two-week washout. This approach is misleading, and conceals the likely possibility that these patients would have done better had they been left on the sulfonylurea.

The reason that the response rate using HbA1c was so much less than using FSG is that HbA1c is a lagging indicator of glycemic control. The level of glycemic control on previous SFU therapy was probably not very different from that achieved with troglitazone, hence little change in HbA1c. Fasting glucose levels, however, changed very rapidly. Deterioration in glucose levels after two weeks without the sulfonylurea sets the stage from which a troglitazone effect can be observed. However, two weeks is reflected little in HBA1c.

For patients on diet alone, one would expect little change in glycemic control during the washout period and hence good agreement in response rate based on HbA1c vs FSG. This was in fact the case. For patients on diet alone, the response rate was 40% for HbA1c and 47% for FSG. Thus, troglitazone monotherapy is not indicated for patients on sulfonylureas, and gives a good response in only about 40% of patients not on sulfonylureas.

Hyperglycemia after a mixed meal was improved by troglitazone. As noted above with FSG, this improvement occurred relative to a baseline value which occurred following discontinuation of previous therapy.

Body weight was increased by troglitazone relative to placebo. On troglitazone there was a mean 1 pound increase in body weight compared to a 7 pound loss on placebo. There were no changes in blood pressure.

TABLE 10 Primary Efficacy Parameters at Month 6: Prestudy Therapy (Diet and Oral Therapy)

Prestudy Parameter / Therapy	Placebo	Troglitazone (mg) 100	200	400	600
DIET ONLY					
HbA_{1C}					
N	18	16	18	19	15
Mean Baseline (SD)	8.7 (1.9)	9.2 (2.0)	8.3 (1.5)	8.5 (2.1)	8.6 (2.2)
Adjusted Mean Change (SE)	0.40 (0.40)	0.48 (0.41)	-0.24 (0.40)	0.34 (0.36)	-0.95 (0.42)
Difference From Placebo		0.08	-0.65	-0.06	-1.35*
95% CI of Difference[a]		(-1.31, 1.47)	(-2.10, 0.81)	(-1.37, 1.24)	(-2.79, 0.08)
Fasting Serum Glucose					
N	18	17	18	19	15
Mean Baseline (SD)	202 (68)	228 (66)	191 (53)	201 (61.1)	201 (56)
Adjusted Mean Change (SE)	-6.2 (14.1)	-6.9 (14.3)	-24.4 (14.2)	-16.6 (12.6)	-48.4 (14.9)
Difference From Placebo		-0.7	-18.2	-10.4	-42.2*
95% CI of Difference[a]		(-49.1, 47.7)	(-69.6, 33.1)	(-56.4, 35.6)	(-92.8, 8.4)
ORAL ANTIDIABETIC THERAPY					
HbA_{1C}					
N	60	62	63	57	64
Mean Baseline (SD)	8.8 (1.7)	8.4 (1.6)	8.7 (1.8)	8.7 (1.74)	8.9 (1.6)
Adjusted Mean Change (SE)	1.86 (0.24)	1.97 (0.24)	1.48 (0.24)	1.06 (0.25)	0.69 (0.24)
Difference From Placebo		0.11	-0.38	-0.80*	-1.17*
95% CI of Difference[a]		(-0.72, 0.94)	(-1.20, 0.44)	(-1.63, 0.04)	(-1.98, -0.35)
Fasting Serum Glucose					
N	61	60	63	57	64
Mean Baseline (SD)	231 (63)	235 (61)	254 (69)	239 (76)	249 (67)
Adjusted Mean Change (SE)	32.7 (7.8)	20.7 (7.9)	-15.7 (7.7)	-28.3 (8.0)	-33.1 (7.7)
Difference From Placebo		-12.0	-48.3*	-60.9*	-65.7*
95% CI of Difference[a]		(-38.8, 14.8)	(-74.8, -21.8)	(-87.8, -34.1)	(-92.0, -39.4)

* $p \leq 0.05$, based on step-down test for linear trend
[a] Via Dunnett's test

TABLE 11. Responders at Month 6: ITT

Responder as Defined by:	Placebo	Troglitazone (mg)			
		100	200	400	600
≥1% Reduction in Hemoglobin A_{1C}[a]					
N	78	78	81	76	79
Responders, N (%)	5 (6)	5 (6)	7 (9)	11 (15)	18 (23)*
≥30 mg/dL Reduction in FSG[a]					
N	79	77	81	76	79
Responders, N (%)	16 (20)	11 (14	31 (38)*	34 (45)*	43 (54)*

[a] From baseline
* $p \leq 0.01$, significantly different from placebo (based on step-down CMH tests)

TABLE 12. Responders at Month 6 ITT: Prestudy Therapy (Diet/Oral Therapy)

Prestudy Therapy	Placebo	Troglitazone (mg)			
		100	200	400	600
Responder as Defined by:					
Oral Antidiabetic Prestudy Therapy					
≥1% Reduction in Hemoglobin A_{1C}[a]					
N	60	62	63	57	64
Responders, N (%)	3 (5)	0 (0)	2 (3)	8 (14)	12 (19)
≥30 mg/dL Reduction in FSG[a]					
N	61	60	63	57	64
Responders, N (%)	11 (18)	6 (10)	24 (38)	26 (46)	36 (56)
Diet Prestudy Therapy					
≥1% Reduction in Hemoglobin A_{1C}[a]					
N	18	16	18	19	15
Responders, N (%)	2 (11)	5 (31)	5 (28)	3 (16)	6 (40)
≥30 mg/dL Reduction in FSG[a]					
N	18	17	18	19	15
Responders, N (%)	5 (28)	5 (29)	7 (39)	8 (42)	7 (47)

[a] From baseline

Safety:

Peripheral edema was reported in 15 (4.6%)troglitazone patients. Seven of these were on 600 mg compared to 3 on 100 mg, 2 on 200 mg and 3 on 300 mg and 0 on placebo. The edema was considered by the investigator to be possibly related to study medication in 3. None of these reports was classified as serious. There were no deaths. Serious events appeared to be randomly distributed between placebo and various doses of troglitazone. Withdrawal because of AE occurred in 4% of placebo patients and 3% of troglitazone patients, including 1 patient with a rash (400 mg) and one with increased liver enzymes(100 mg). 11 other patients on various doses of troglitazone had minor increases in liver enzymes which returned to normal by the end of the study despite continuation of the drug. The small decrease in hematocrit observed in other studies was observed here as well. One patient had a significant rise in LDH.

Conclusion:

This study provides little support for the indication of troglitazone as monotherapy. It is clear from the data that switching patients from SFU monotherapy to troglitazone monotherapy leads to deterioration in glycemic control. With respect to patients not on previous drug therapy, troglitazone resulted in a statistically significant fall in HbAlc only at a dose of 600 mg in a group of only 15 patients. Although the proposed label indicates a starting dose of 400 mg, this dose showed no effect. The 200 mg dose. However, was associated with HbAlc and FSG treatment effects that approach statistical significance.

Patient characteristics at baseline are shown in the table. Several points are of note. Although the number of black patients was small, the percent of black patients who responded was at least as great as in white patients. No difference was observed between responders and non-responders with respect to C peptide level. The responders tended to be older and in poorer control than the non-responders, as measured by higher HbA1c and FSG. It was not stated if these differences were statistically significant.

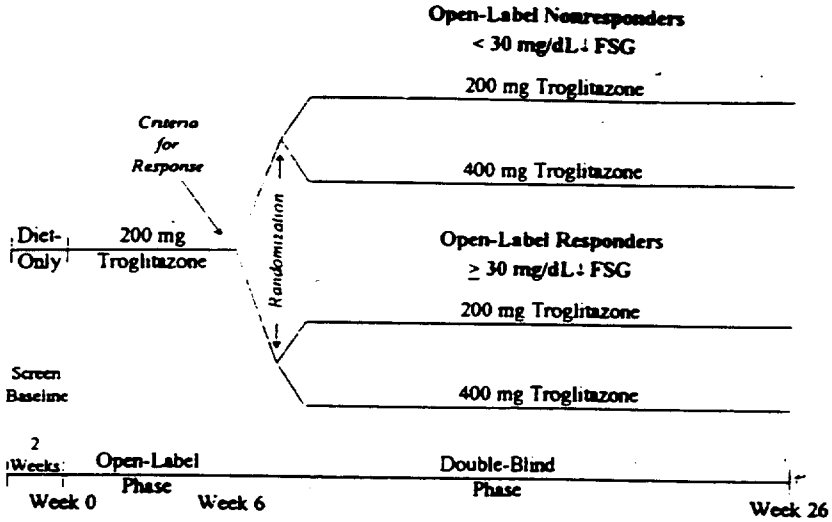
TABLE 4 Summary of Patient Characteristics at Baseline
(Intent-to-Treat Population)
(Page 1 of 2)

	Open-Label Nonresponder		Open-Label Responder		
	CI-991 200 mg/day N = 88	CI-991 400 mg/day N = 95	CI-991 200 mg/day N = 41	CI-991 400 mg/day N = 32	Total N = 256
Sex N (%)					
Men	45 (51.1)	54 (56.8)	23 (56.1)	21 (65.6)	143 (55.9)
Women	43 (48.9)	41 (43.2)	18 (43.9)	11 (34.4)	113 (44.1)
Postmenopausal	28 (31.8)	29 (30.5)	9 (22.0)	6 (18.8)	72 (28.1)
Race N (%)					
White/Caucasian	76 (86.4)	82 (86.3)	35 (85.4)	25 (78.1)	218 (85.2)
Black	8 (9.1)	6 (6.3)	4 (9.8)	5 (15.6)	23 (9.0)
Hispanic	2 (2.3)	3 (3.2)	1 (2.4)	0 (0.0)	6 (2.3)
Asian	2 (2.3)	3 (3.2)	1 (2.4)	2 (6.3)	8 (3.1)
Other	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)
Age (yr)					
Mean	56.4	56.9	52.3	54.0	55.6
SD	10.4	10.6	11.1	9.0	10.5
Median	57.0	56.0	53.0	54.0	56.0
Min, Max	34.0, 79.0	31.0, 79.0	26.0, 75.0	34.0, 75.0	26.0, 79.0
< 65 years N (%)	65 (73.9)	69 (72.6)	37 (90.2)	30 (93.8)	201 (78.5)
≥ 65 years N (%)	23 (26.1)	26 (27.4)	4 (9.8)	2 (6.3)	55 (21.5)
Duration of Diabetes (yr)					
Mean	5.4	5.1	6.3	3.4	5.2
SD	5.2	5.6	6.9	3.1	5.5
Median	3.0	3.0	4.0	2.0	3.0
Min, Max	0.0, 25.0	0.0, 32.0	0.0, 27.0	0.0, 10.0	0.0, 32.0

057

991-057 - Responder Analysis without Placebo Control

The purpose of this study was to determine if patients who did not respond to a daily dose of 200 mg troglitazone would respond to 400 mg. Patients were type 2 diabetics with HbA1c over the upper limit and fasting C peptide of at least 1.5 ng/dl. 69% of patients were on a sulfonylurea at the time of screening but the dose could not exceed ½ the maximal recommended dose. The SFU was discontinued during a two week run-in period. Patients were then treated with 200 mg of troglitazone open-label for 6 weeks. Those with a fall in FSG of less than 30 mg/dl are designated as non-responders. Those with a fall of at least 30 mg/dl are designated responders. Responders and non-responders are then treated for 20 weeks in double blind fashion with 200 or 400 mg troglitazone. A schematic diagram of the study is shown below:



057

FIGURE 1. Study Design

TABLE 4. Summary of Patient Characteristics at Baseline
(Intent-to-Treat Population)
(Page 2 of 2)

	Open-Label Nonresponder		Open-Label Responder		
	CI-991 200 mg/day N = 88	CI-991 400 mg/day N = 95	CI-991 200 mg/day N = 41	CI-991 400 mg/day N = 32	Total N = 256
Body Mass Index (kg/m^2)					
Mean	33.5	32.6	33.3	33.4	33.1
SD	8.5	7.0	5.7	6.4	7.2
Median	31.0	31.4	32.4	32.6	31.5
Min, Max					
Waist-Hip Ratio (cm)					
Mean	0.9	0.9	1.0	1.0	1.0
SD	0.1	0.1	0.1	0.1	0.1
Median	0.9	0.9	1.0	1.0	1.0
Min, Max					
Fasting Serum Glucose (mg/dL)					
Mean	235.4	238.0	276.2	275.9	248.0
SD	62.9	64.5	70.9	98.5	71.9
Median	227.0	236.0	286.0	250.5	236.5
Min, Max					
Hemoglobin A_{1c} (%)					
Mean	8.7	8.7	9.5	9.8	9.0
SD	1.8	1.6	1.9	2.5	1.9
Median	8.6	8.4	9.4	9.3	8.6
Min, Max					
C-Peptide (ng/mL)					
Mean	3.2	3.3	3.4	4.0	3.4
SD	1.3	1.4	1.0	2.4	1.5
Median	3.0	3.0	3.2	3.4	3.1
Min, Max					

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A summary of the results of the 20 weeks of blinded treatment is shown in table 8 on the following page. This table illustrates several important points. First, and most important is that only 73 patients of the 256 patients(21.5%) could be classified as initial responders to 200 mg troglitazone using fall in fasting glucose of 30 mg/dl as the criterion for response. Even in those responders, continuation of the 200 mg dose did not result in a significant fall in HbAlc. An effect on HbAlc was only observed with 400 mg. The disparity between response based on fasting glucose vs. HbAlc, and the failure of low dose troglitazone to reduce HbAlc is consistent with the findings of study 032, the six month controlled study of troglitazone monotherapy described previously. As shown below, a small increase in body weight was observed in responders on 400 mg trogltiazone compared to decreases in body weight in the other groups.

	Non-responders		Responders	
Change	200mg	400 mg	200 mg	400 mg
HbalC	1.02	0.89	-0.16	-0.99
FSG	+1.6	-15.3	-43	-72
Wt, lbs	-3.5	-1.9	-0.5	+0.5
N=	88	95	41	32

In response to my request, PD submitted additional data on April 14 and 18, 1997 on the patients who had not previously been on an antidiabetic medication. These results are summarized in the second table on p15. Of 46 such patients, 20(45%) were classified as "responders" to 200 mg troglitazone and 26 patients (55%) were classified as non-responders. There were 13 patients, who went on to receive 400 mg after having been classified as non-responders to 200 mg. Again, basing a positive response on a fall in FSG of 30 mg/dl, I found three patients, #404, #418, and #453 who responded to 400 mg. In addition, these patients experienced fall is HbAlc over 26 weeks of 1.6%, 1.8% and 2.9% respectively. Therefore, 3/13 (23%) patients responded to 400 mg who did not respond adequately to 200 mg. Thus, the 55% of patients who were non-responders to the initial 200 mg dose could probably be reduced to 42% by increasing the dose to 400 mg. The numbers are small, but are consistent with the results of Study 032 discussed above. Taken together these studies indicate that about half of previously untreated patients will get a good response to troglitazone with a fall of FSG of greater than 30 mg/dl and a fall in HbAlc of 1.0% or more at 400 mg.

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TABLE 8. Summary of Change from Baseline at Week 26
(Intent-to-Treat)

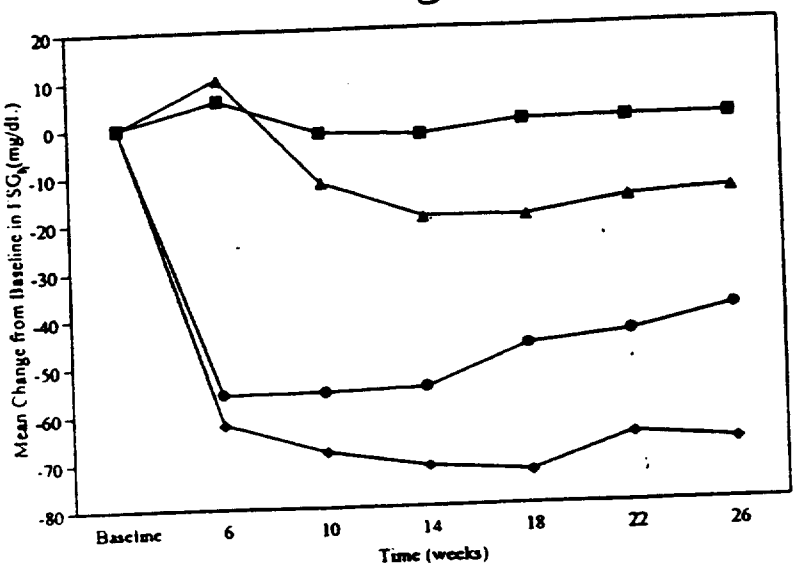
Parameter	Open-Label Nonresponders		Open-Label Responders	
	200 mg/day N = 88	400 mg/day N = 95	200 mg/day N = 41	400 mg/day N = 32
Hemoglobin A_{1c} (%)				
Baseline Mean (SD)	8.7 (1.76)	8.67 (1.58)	9.54 (1.85)	9.83 (2.46)
Adjusted Change from Baseline (SE)	1.02 (0.19)	0.89 (0.18)	-0.16 (0.26)	-0.99 (0.29)
Difference from 200 mg/day (SE)		-0.13 (0.25)		-0.84 (0.38)
95% Confidence Interval		(-0.63, 0.37)		(-1.59, -0.08)
p Value		0.605		0.030*
Fasting Serum Glucose, (mg/dL)				
Baseline Mean (SD)	235.38 (62.88)	238.01 (64.50)	276.17 (70.94)	275.94 (98.52)
Adjusted Change from Baseline (SE)	1.64 (6.03)	-15.32 (5.74)	-43.00 (7.41)	-72.00 (8.52)
Difference from 200 mg/day (SE)		-16.96 (8.00)		-29.00 (10.81)
95% Confidence Interval		(-32.76, -1.15)		(-50.64, -7.36)
p Value		0.036*		0.010*

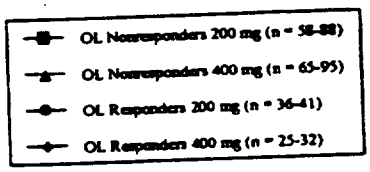
* Statistically significant at 0.05 significance level based on ANCOVA with treatment and center as factors and baseline as covariate

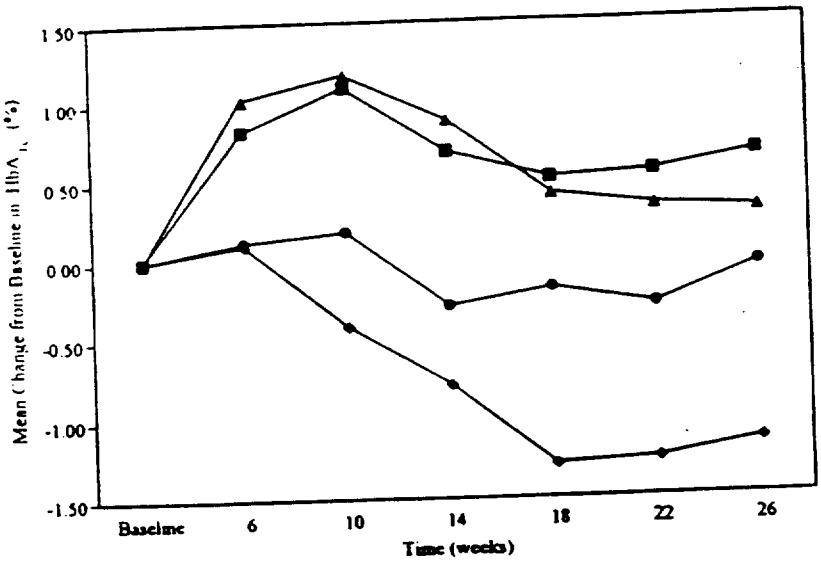
Study 057 20+6 weeks
Patients on Diet Alone

	NR	NR	Responder	Responder
dose	200mg	400mg	200mg	400mg
n=	13	13	11	9
FSG, change	21	-22	-14	-64
mg/dl SD	76	54	39	27
A1c, change%	0.08	-0.52	-0.90	-2.09
SD	1.50	1.35	1.45	1.38

057







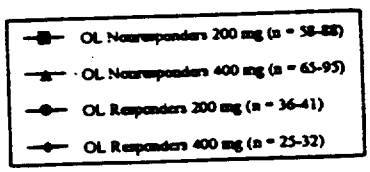


FIGURE 2. Mean Change from Baseline for HbA_{1c} and FSG: All Available Data

057

991-031: 12 Weeks double blind dose response study in NIDDM

Patients were included with HbA1c between 7 and 11% and C peptide of at least 1.1 ng/ml. 80% of patients had been taking an oral antidiabetic medication which was stopped before the run-in. The mean age was 57.5 years and the average duration of diabetes was 6.9m years. Mean FSG at baseline was 247 mg/dl and mean HbA1c at baseline was 9.2 % As shown in the figure, there was a four week diet-only run-in followed by randomization to placebo or 200, 400, 600, 800 mg troglitazone. Pharmacokinetics measurements were also performed as described later. It should be noted here, for the sake of comparison with other studies, that the formulation employed in this study had reduced bioavailability. For purposes of comparison, 800 mg employed in this study is approximately equal to 600 of the to-be-marketed formulation.

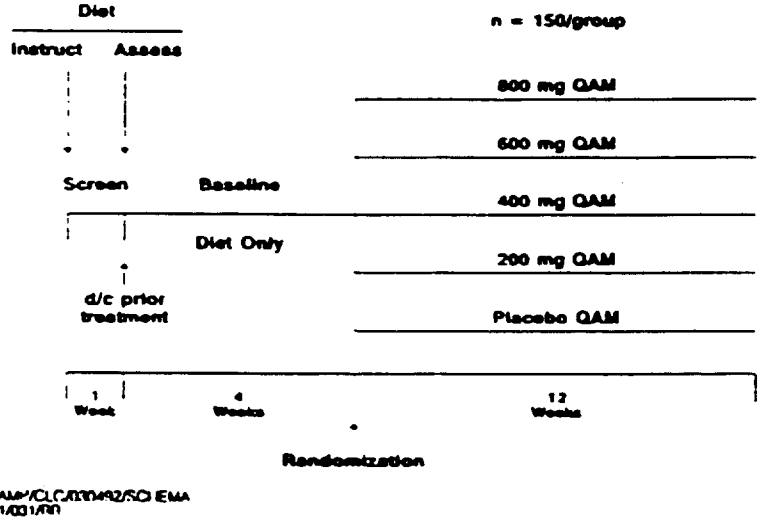


FIGURE 1. Study Design (991-031)

Efficacy:

13% of patients dropped out overall because of lack of efficacy. An intent -to- treat analysis is shown in the table. Placebo patients experienced increases in serum glucose, fructosamine, and HbA1c. All doses of troglitazone were different from placebo. However, the primary effect of the drug was to blunt the deterioration of glucose control which occurred in the placebo patients. Even at 800 mg of Troglitazone, there was still a rise in HbA1c above baseline, 1.24% in placebo patients vs. 0.21% at 800 mg troglitzone. As had been observed in studies discussed previously, troglitazone was more effective in lowering FSG vs HbA1c. As expected, effects on fructosamine were intermediate between FSG and HbA1c.

In response to my request of April 7th, PD made a submission on April 14 in which they analyzed patients according to whether they had previously been taking antidiabetic medication. Since 83% of patients had been on a previous antidiabetic medication (77% on an oral agent alone, 3% on insulin, and 3% on combination oral agent with insulin), mean data from this group is very similar to that of the entire group. As shown in figures 5&9, withdrawal of the previous antidiabetic medication resulted in deterioration of glycemic control which was only partially reversed by troglitazone. However, troglitazone did improve glycemic control in previously untreated patients. These results are shown in the two bar graphs(figs 2&6). Although PD has not submitted a formal statistical analysis of these data, it would appear that all doses of troglitazone were superior to placebo, but there was little difference among the different doses of troglitazone. At 800 mg, the treatment effect for HbA1c (change from baseline minus placebo) was -0.78%. At 600 mg, the treatment effect was -0.69%. Considering all four doses of troglitzone, the total data base from this study of troglitazone-treated patients who were previously on diet alone is n=94.

Adverse events:

There appeared to be dose-dependent increase in nervous system AE's. These were reported in 24% of patients on 800 mg, 19% of patients on 600 mg, and 14% of patients on 400 mg compared to 11% in patients on 200 mg and placebo. Looking at nervous system AE's reported to be associated with the drug, there were 13% at 800 mg, 10% at 600 mg compared to 5% in placebo. Dizziness was the most common AE. A nervous system AE which resulted in discontinuation of treatment was reported in 4 patients on 800 mg, 3 patients on 600 mg and 2 patients on placebo. 10% of

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Study 031

RR 720-03368

TABLE 10. Primary Efficacy Parameters at Last Available Visit: Intent-to-Treat Population

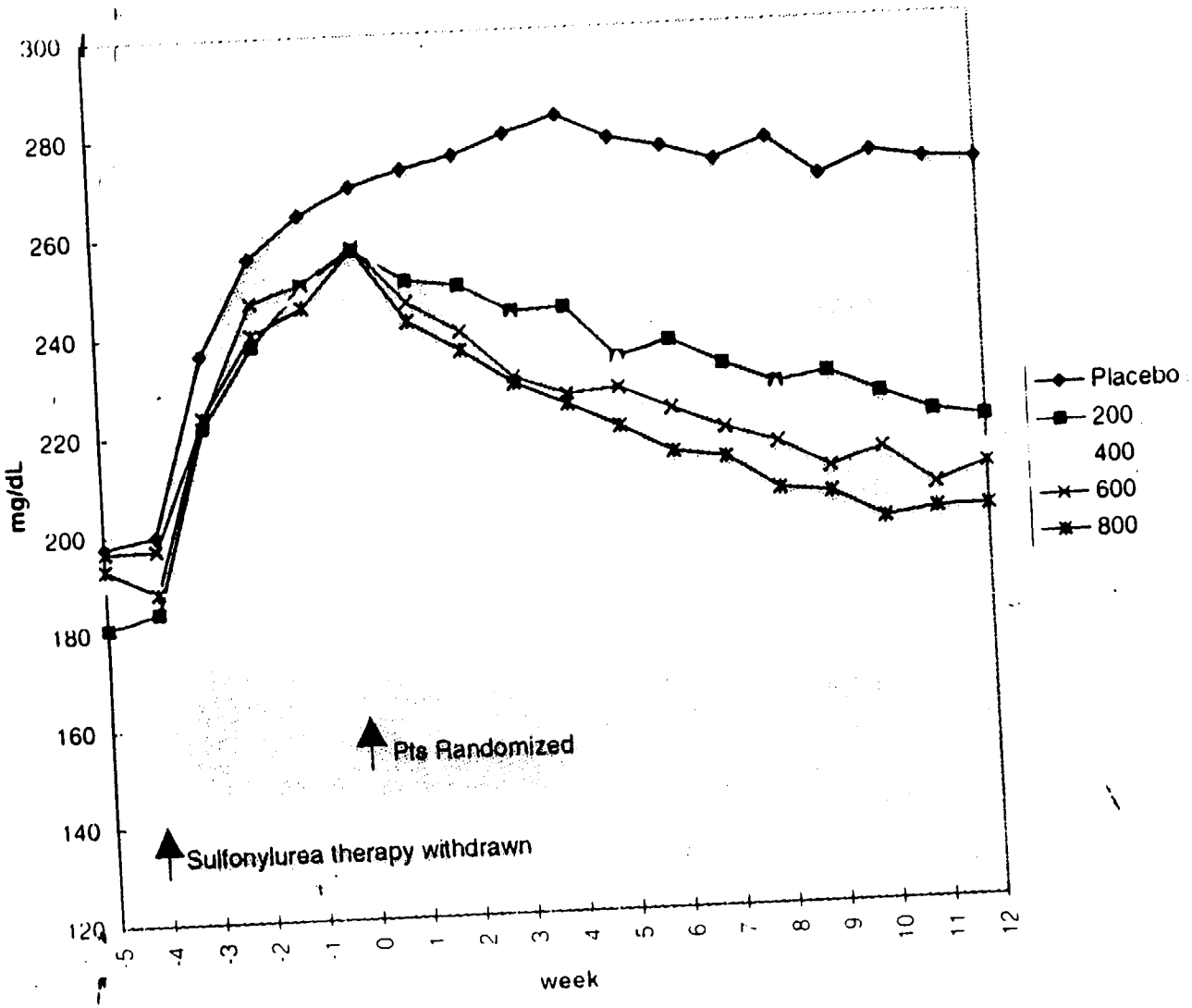
Parameter	Placebo N = 157	Troglitazone 200 mg N = 157	Troglitazone 400 mg N = 156	Troglitazone 600 mg N = 162	Troglitazone 800 mg N = 158
Fasting Serum Glucose, mg/dL					
Mean Baseline	254.9	242.1	245.3	243.7	249.0
Adjusted Mean Change From Baseline	15.3	-21.0	-27.0	-32.1	-42.8
Adjusted Mean Difference From Placebo[a] (95% Confidence Interval)[a]	NA	-36.2* (-47.1, -25.4)	-42.3* (-53.2, -31.4)	-47.4* (-58.2, -36.6)	-58.1* (-68.9, -47.2)
Hemoglobin A_{1C}, %					
Mean Baseline	9.46	9.16	9.15	9.21	9.28
Adjusted Mean Change From Baseline	1.24	0.57	0.53	0.23	0.21
Adjusted Mean Difference From Placebo[a] (95% Confidence Interval)[a]	NA	-0.68* (-0.98, -0.38)	-0.71* (-1.01, -0.42)	-1.01* (-1.31, -0.72)	-1.03* (-1.33, -0.73)
Fructosamine, µmol/L					
Mean Baseline	398.7	382.2	385.8	385.0	395.0
Adjusted Mean Change From Baseline	46.3	14.3	8.9	0.8	-7.2
Adjusted Mean Difference From Placebo[a] (95% Confidence Interval)[a]	NA	-32.0* (-45.0, -19.0)	-37.4* (-50.4, -24.4)	-45.5* (-58.4, -32.6)	-53.5* (-66.4, -40.5)

[a] Based on ANCOVA model (with treatment and center effects and baseline as covariate). Negative differences indicate larger reductions in troglitazone group compared with placebo.

* $p < 0.001$ (based on step-down tests for trend and Dunnett's Test, 2-sided).

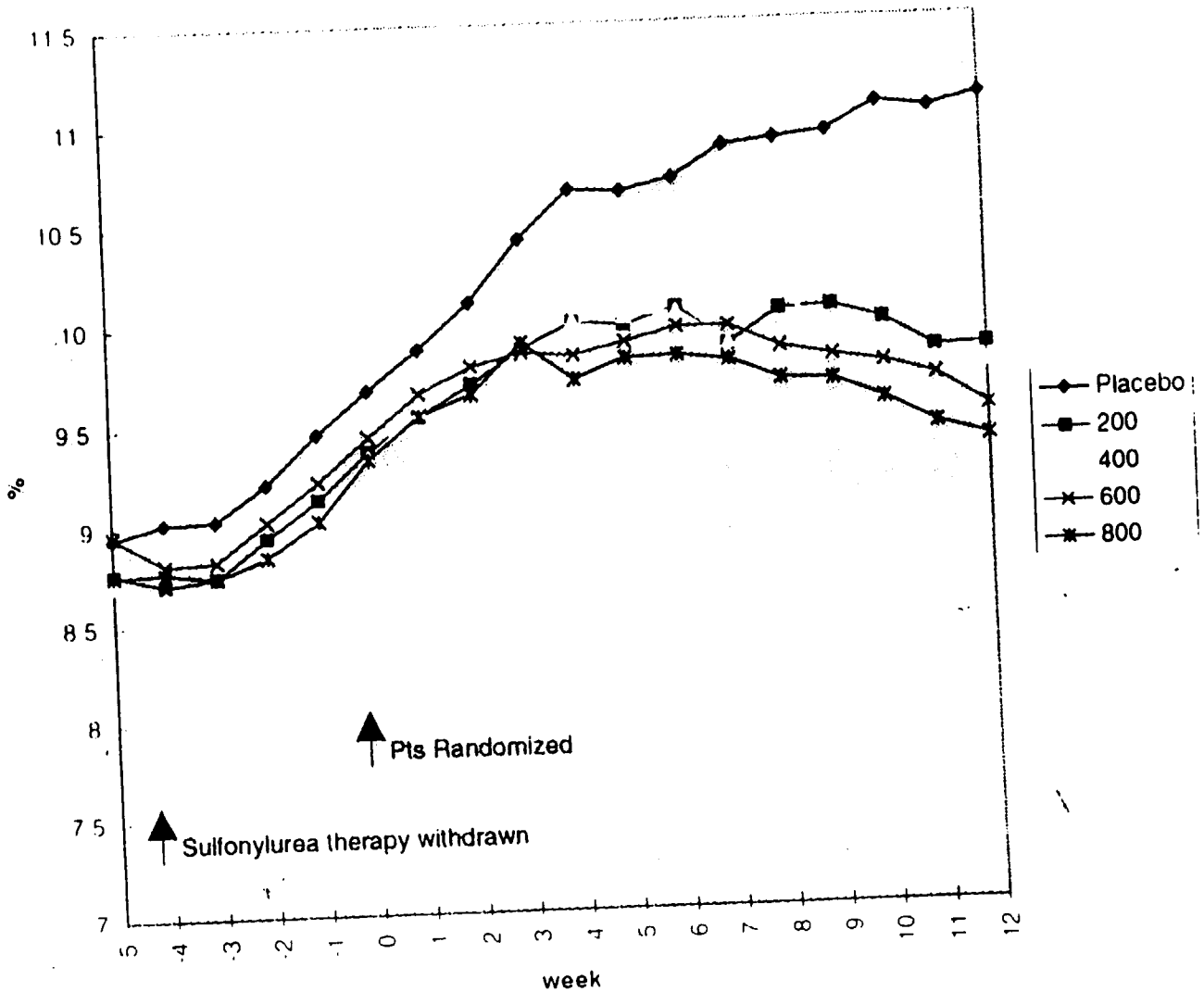
Study 031.

Figure 5. FSG: Oral-Agent Pretreated Patients



Study 031

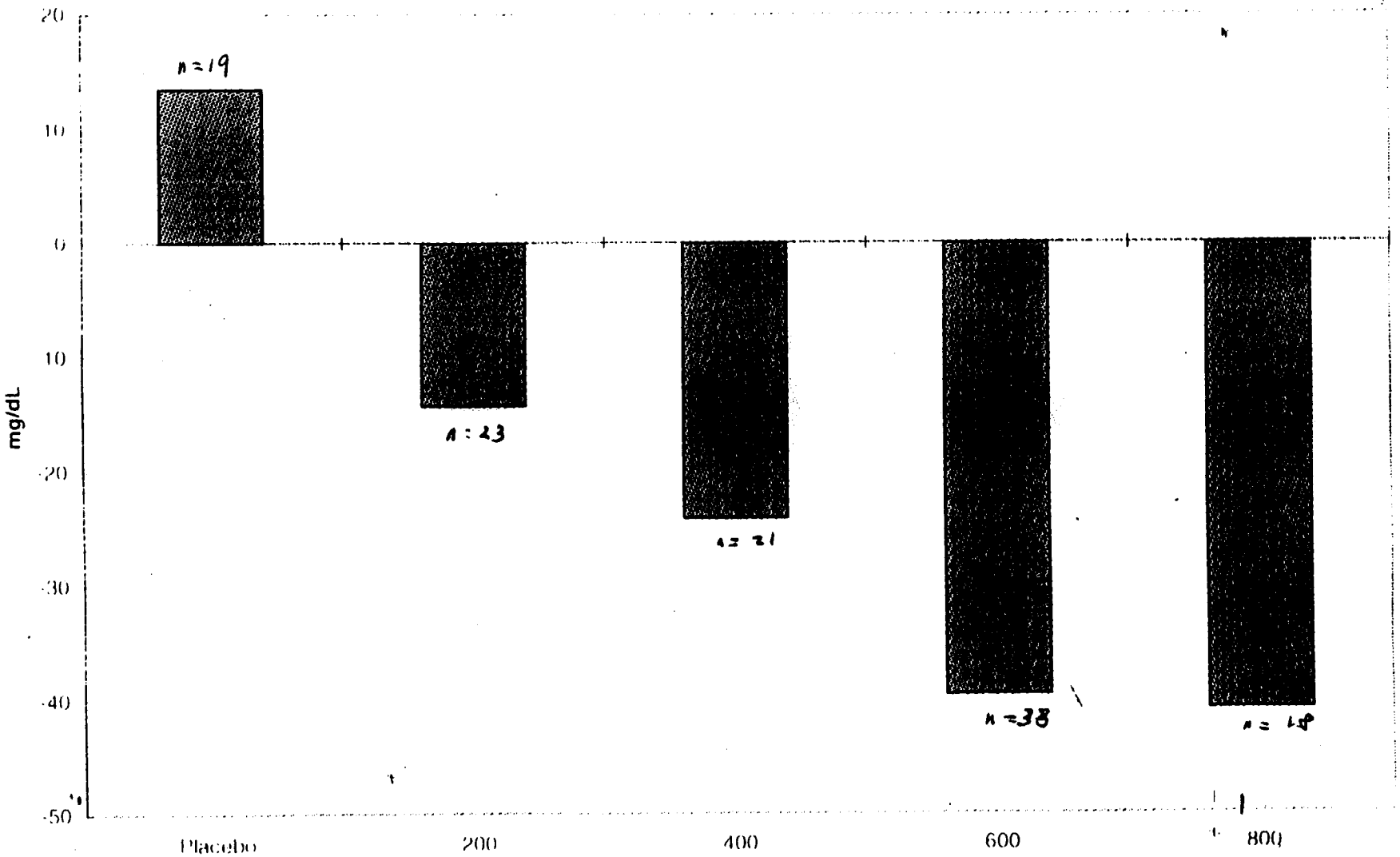
Figure 9. HbA1c: Oral-Agent Pretreated Patients



12 weeks

Figure 2. FSG Change from Baseline: Diet-Only Pretreated Patients

Study 031



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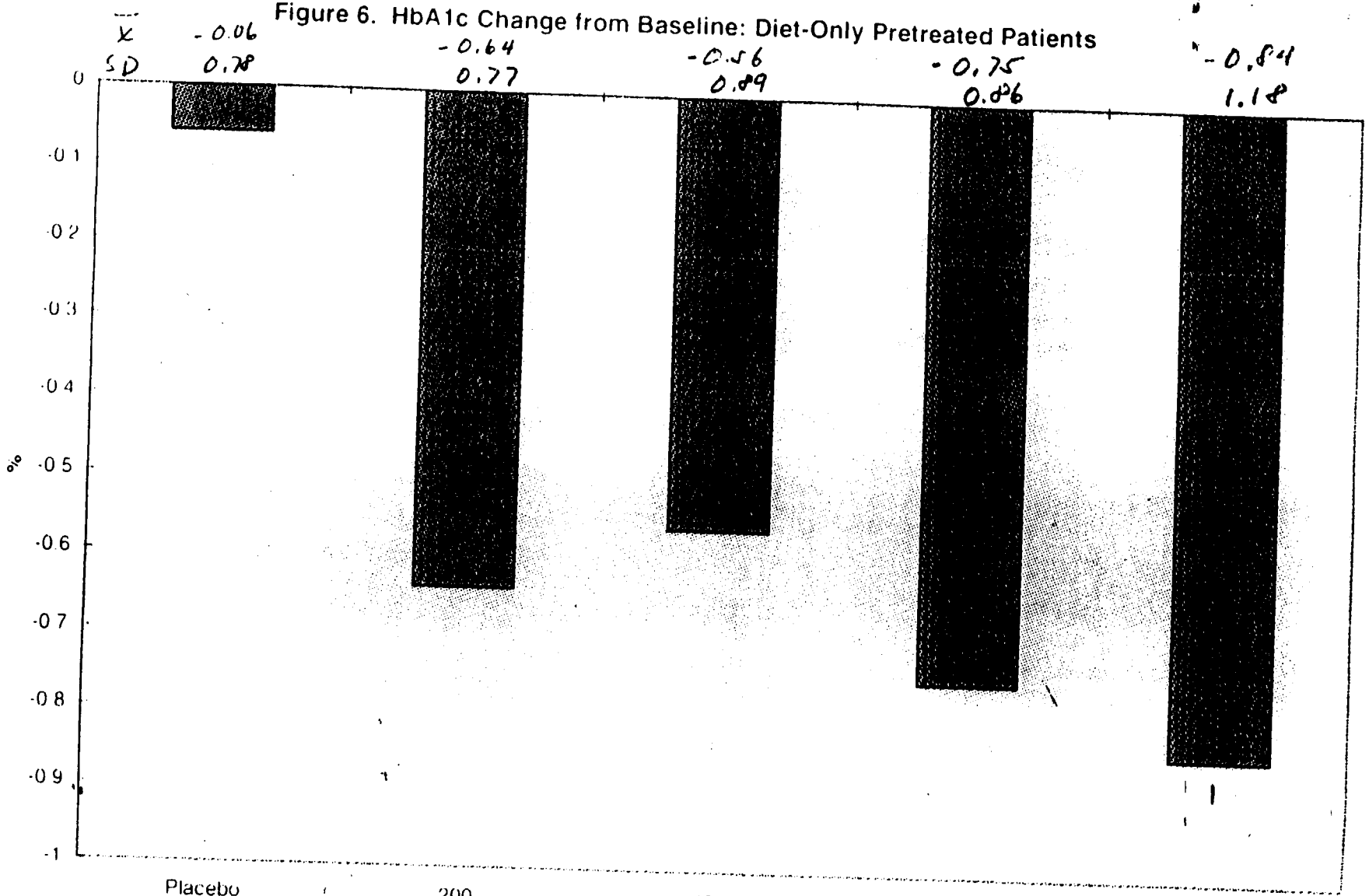
Study 031

Figure 6. HbA1c Change from Baseline: Diet-Only Pretreated Patients



N = 19 23 20 [illegible] 15

Rx effect 0 -0.58% -0.50% -0.69% -0.75%

patients on 800 mg troglitzone withdrew because of an AE compared to 5% of patients on placebo. AE's of the digestive system were the most common AE associated with withdrawal of medication. This occurred in 5 % of patients on 800 mg, 2% at 600 mg, 3% at 400 mg and none at 200 mg or placebo. These AE's were abnormal LFT's, nausea, vomiting, etc. Among changes in laboratory tests were the fall in hematocrit and WBC reported in other studies. In addition, an atrial natriuretic factor increased in a dose-dependent fashion as follows: 0.7, 4.7, 4.1, 5.35, 6.6 pg/ml at 0, 200, 400, 600 and 800 mg respectively. 20% of patients at 800 mg developed a "high" ANF value which had been normal at baseline. 11% of placebo patient developed a "high" ANF which had been normal at baseline.

Pharmacokinetic data are shown in table 14 and figure 8. The t max was about 3 hours and t ½ was about 14 hours. The C max was about 1 ug/ml at 400 mg and was roughly proportional at other doses. The concentration of metabolite 3 was about the same as unchanged drug. The concentration of metabolite 1 was roughly five times higher at all doses.

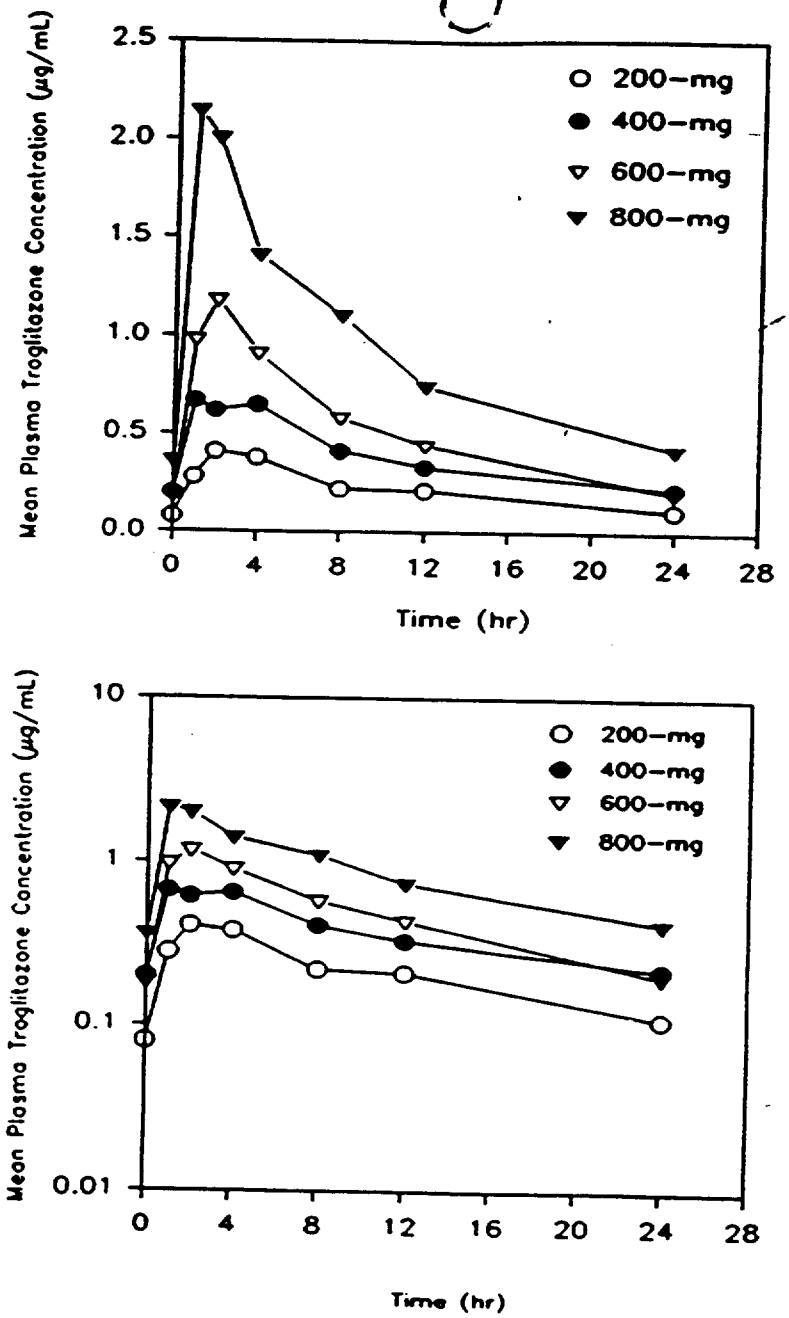


FIGURE 8. Mean Week 12 Troglitazone Plasma Concentration-Time Profile Following Administration of 200-, 400-, 600-, and 800-mg Troglitazone Tablets Once Daily For 12 Weeks (upper figure is linear scale, lower figure is semi-logarithmic scale)

TABLE 14. Mean (%RSD) Week 12 Pharmacokinetic Parameter Values of Troglitazone, Metabolite 1, and Metabolite 3 Following Administration of Troglitazone Tablets Once Daily For 12 Weeks
(Page 1 of 2)

Dose/ Parameter	Troglitazone	Metabolite 1	Metabolite 3
Troglitazone 200 mg			
N = 14			
Cmax	0.52 (52)	2.57 (62)	0.47 (53)
NCmax	0.52	2.57	0.47
tmax	3.4 (84)	7.4 (106)	3.5 (80)
AUC(0-24)	5.29 (48)	41.28 (43)	5.54 (54)
NAUC	5.29	41.28	5.54
CL/F	685 (55)	ND	ND
λz	0.051 (56)	ND	ND
t½	16.8 (43)	ND	ND
AUC Ratio	ND	7.80	1.05
Troglitazone 400 mg			
N = 15			
Cmax	0.96 (52)	5.36 (74)	0.98 (71)
NCmax	0.48	2.68	0.49
tmax	4.0 (79)	5.2 (74)	3.7 (56)
AUC(0-24)	9.03 (40)	83.4 (68)	11.22 (59)
NAUC	4.52	41.70	5.61
CL/F	848 (38)	ND	ND
λz	0.061 (62)	ND	ND
t½	14.6 (44)	ND	ND
AUC Ratio	ND	9.24	1.24

Cmax = Maximum plasma concentration (μg/mL).
NCmax = Cmax values normalized to the 200-mg dose.
tmax = Time for Cmax (hours).
AUC(0-24) = Area under plasma concentration-time curve (μg·hr/mL) from time zero to 24 hours postdose.
NAUC = AUC(0-24) values normalized to the 200-mg dose.
CL/F = Apparent oral clearance (mL/min).
λz = Terminal elimination rate constant (hr^{-1}).
t½ = Elimination half-life (hr).
AUC Ratio = Ratio of mean AUC(0-24) of Metabolite 1 or Metabolite 3 to mean AUC(0-24) of troglitazone.
ND = Not determined.

TABLE 14. Mean (%RSD) Week 12 Pharmacokinetic Parameter Values of Troglitazone, Metabolite 1, and Metabolite 3 Following Administration of Troglitazone Tablets Once Daily For 12 Weeks
(Page 2 of 2)

Dose/ Parameter	Troglitazone	Metabolite 1	Metabolite 3
Troglitazone 600 mg			
N = 18			
Cmax	1.42 (73)	6.54 (65)	1.13 (63)
NCmax	0.47	2.18	0.38
tmax	2.4 (91)	5.5 (61)	4.1 (75)
AUC(0-24)	12.09 (50)	93.51 (55)	12.79 (46)
NAUC	4.03	31.17	4.26
CL/F	1080 (60)	ND	ND
λz	0.066 (36)	ND	ND
t½	11.9 (40)	ND	ND
AUC Ratio	ND	7.73	1.06
Troglitazone 800 mg			
N = 13			
Cmax	2.48 (56)	14.58 (60)	2.37 (46)
NCmax	0.62	3.65	0.59
tmax	2.6 (97)	4.3 (62)	3.2 (73)
AUC(0-24)	22.39 (31)	207.79 (55)	26.89 (28)
NAUC	5.60	51.95	6.72
CL/F	666 (40)	ND	ND
λz	0.064 (44)	ND	ND
t½	12.3 (35)	ND	ND
AUC Ratio	ND	9.28	1.20

Cmax = Maximum plasma concentration (μg·mL).
NCmax = Cmax values normalized to the 200-mg dose.
tmax = Time for Cmax (hours).
AUC(0-24) = Area under plasma concentration-time curve (μg · hr/mL) from time zero to 24 hours postdose.
NAUC = AUC(0-24) values normalized to the 200-mg dose.
CL/F = Apparent oral clearance (mL/min).
λz = Terminal elimination rate constant (hr^{-1}).
t½ = Elimination half-life (hr).
AUC Ratio = Ratio of mean AUC(0-24) of Metabolite 1 or Metabolite 3 to mean AUC(0-24) of troglitazone.
ND = Not determined.

Dose Response Study

In response to requests for additional data on the use of troglitazone in patients who had not previously been on oral hypoglycemic agents, PD submitted a new analysis of this study on May 14, 1997, separating patients who had previously been on oral agents from those who had not. This study was a 28 week dose-escalation. Group 1 received 200 mg for 28 weeks. Group 2 received 200 mg for 8 weeks followed by 400 mg for 20 weeks. Group 3 received 200 mg for 8 weeks, 400 mg for 8 weeks and 600 mg for 12 weeks. There were about 30 patients in each group. After 28 weeks the fall in glucose was 40 mg/dl in groups 1 and 2 and 34 mg/dl in group 3. Since the mean fall in glucose was actually a bit less in patients who received 600 mg, these data do not support this type of dose escalation regimen. On the contrary, lack of a dose-response realtionship would make one question whether the drug was active at all, particuarly because there was no placebo group for comparison. Thus this study does not provide any additional support for the use of troglitazone in patients previously not on drug therapy. By contrast, dose escalation did have an effect in patients previously on oral antidiabetic medication, although even here the effects were small. Decreases from baseline of 27, 23, and 47 mg/dl were observed in patients whose final dose were 200, 400, and 600 mg respectively.

Study 042 - Safety Study with Cardiac Function - 96 Week Comparison Of Troglitazone with Glyburide

In view of animal studies showing that troglitazone caues cardiomegaly, this clinical study was undertaken to determine if high dose trogltiazone affects cardiac size and function in diabetic patients in comparison to Glyburide. The study was undertaken in two parts, a 48 week primary study followed by a 48 week extension study. A scheme for the 48 week primary study is shown below. Although designed as a safety study of troglitazone vs Glyburide, this study also provides important comparative information about efficacy.

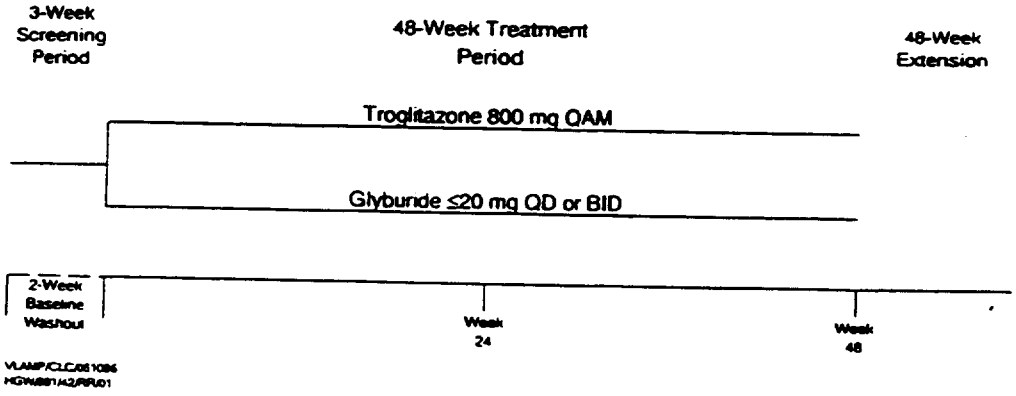


FIGURE 1. Study Design

042

Patients are taken off their previous antidiabetic medication for two weeks in order to establish a new baseline. They are then treated with either 800 mg of troglitazone (equivalent to 600 mg of current formulation) or a glyburide titration. The median final dose of glyburide, 15 mg. Since the purpose of the study was to compare the cardiac effects of high dose trogltiazone vs Glyburide, patients chosen for this study had more advanced diabetes than those in other studies 93% of patients had previously been on antidiabetic medication. Approximately 10% had been on insulin, 3% alone and 7% with a sulfonylurea. About 90 had been on a sulfonylurea. Their median age was 54 years with a 6.4 mean duration of diabetes. Mean HbA1c was 9.1%. Other baseline parameters are shown in the table.

032

TABLE 1 Patient Characteristics at Baseline for All Patients
(Page 2 of 2)

	Treatment				Total	
	Troglitazone N = 77		Glyburide N = 77		N = 154	
Waist-Hip Ratio, cm						
Mean (SD)	0.9	(0.1)	0.9	(0.1)	0.9	(0.1)
Median (Min, Max)	0.9		0.9		0.9	
Left Ventricular Mass Index, g/m^2						
Mean (SD)[b]	76.8	(11.1)	78.2	(9.7)	77.5	(10.4)
Median (Min, Max)	77.7		76.5		76.8	
Cardiac Index, L/min/m^2						
Mean (SD)	2.3	(0.4)	2.3	(0.4)	2.3	(0.4)
Median (Min, Max)	2.3		2.4		2.3	
Stroke Volume Index, mL/m^2						
Mean (SD)	32.0	(4.6)	34.0	(4.9)	33.0	(4.9)
Median (Min, Max)	32.0		33.2		32.4	
Fasting Serum Glucose, mg/dL						
Mean (SD)	252.4	(80.6)	256.8	(67.9)	254.6	(74.3)
Median (Min, Max)	264.0		267.0		264.0	
Hemoglobin A_{1C}, %						
Mean (SD)	9.0	(1.6)	9.1	(1.4)	9.1	(1.5)
Median (Min, Max)	9.2		9.2		9.2	
Total Insulin, µIU/mL						
Mean (SD)	16.7	(14.3)	15.7	(11.5)	16.2	(12.9)
Median (Min, Max)	11.2		12.3		12.0	
C-Peptide, ng/mL						
Mean (SD)	2.7	(1.2)	2.7	(1.1)	2.7	(1.2)
Median (Min, Max)	2.3		2.7		2.4	

SD = Standard deviation.
[b] LVMI normal range for men is 63 to 89 g/m^2, and for women in 55 to 75 g/m^2

Disposition of patients is reported by the Sponsor in the table below. Although 77 patients started the study in both groups, only 29 troglitazone patients completed the study compared to 45 Glyburide patients.

042

TABLE 2. Duration of Exposure to Study Medication [Number (%) of Patients]

Completed at Least	Troglitazone 800 mg QD N = 77	Glyburide N = 77
12 Weeks	59 (77)	71 (92)
24 Weeks	53 (69)	70 (91)
36 Weeks	47 (61)	69 (90)
48 Weeks	46 (60)	68 (88)
60 Weeks	34 (44)	55 (71)
72 Weeks	31 (40)	50 (65)
84 Weeks	30 (39)	48 (62)
96 Weeks	29 (38)	45 (58)
>96 Weeks[a]		4 (5)

[a] Exposure >96 weeks occurred as a result of patient visits that were delayed past the end of Week 96.

As shown below, the increased the dropout rate was higher with troglitazone at all time periods, but most dramatic during the first 48 weeks (data below was derived from previous table):

	Trogl	Trogl	Glyburide	Glyburide
	# drop-outs	%	# drop-outs	%
0-12 weeks	18	24%	6	8%
12-48	13	22%	3	4%
48-96	17	37%	23	34%

Thus of the 59 patients who entered week 12 on troglitazone, 13(22%) dropped out by week 48. Of the 71 patients who entered

week 12 on Glyburide, 3 patients(4%) dropped out by week 48.

The reasons why patients dropped out are shown in the following table. During the first 48 weeks of treatment, 18 troglitzone patients withdrew because of lack of efficacy compared to 3 glyburide patients. 11 troglitazone patients withdrew because of an adverse event compared to three glyburide patients. Thus, during the first 48 weeks of treatment, troglitazone was clearly less effective and less safe than was glyburide. The drop-out rate during the second 48 weeks of treatment was lower than during the first and the two drugs were approximately equal.

Of the 35 patients on troglitazone who entered the 48 week extension, 4 patients (11%) withdrew compared to 5 (9%) of the 53 glyburide patients. 6 glyburide patients withdrew for an adverse event compared to one troglitazone patient. However, two of these glyburide patients withdrew because of hypoglycemia, which under ordinary practice would have been handled by decreasing the dose. Glycemic parameters are shown in table 13. The Sponsor claims that these data show that the hypoglycemic activity of troglitazone is sustained for 96 weeks, in comparison to glyburide whose hypoglycemic activity appeared to diminish over time. However, it must be born in mind that many of the troglitazone patients had been withdrawn early in the study because of lack of efficacy, and three of the glyburide patients had been withdrawn because of hypoglycemia. Thus the very patients whose data would have pointed to the superiority of glyburide, were no longer in the cohort which completed the study.

Cardiac Parameters:

Changes in cardiac parameters are found in the two tables on p24b. Of the patients completing the study, there were decreases in left ventricular mass index, cardiac index, and stroke volume index in glyburide-treated patients, compared to troglitazone-treated patients. There was a 3 mm Hg fall in mean arterial blood pressure with troglitazone compared to Glyburide which was associated with a decrease in peripheral resistance although neither achieved statistically significance.

Study 042

TABLE 3. Patient Disposition
[Number (%) of Patients][a]

	Initial Study						Extension					
	Troglitazone		Glyburide		Total		Troglitazone		Glyburide		Total	
Randomized to Treatment	77		77		154		NA	NA	NA	NA	NA	NA
Did Not Enter Extension[b]	NA	NA	NA	NA	NA	NA	11 (14.3)		10 (13.0)		21 (13.6)	
Entered Extension	NA	NA	NA	NA	NA	NA	35 (45.5)		58 (75.3)		93 (60.4)	
Withdrew												
Lack of Efficacy	18 (23.4)		3 (3.9)		21 (13.6)		4 (5.2)		5 (6.5)		9 (5.8)	
Adverse Event	11 (14.3)		3 (3.9)		14 (9.1)		1 (1.3)		6 (7.8)		7 (4.5)	
Other	2 (2.6)		3 (3.9)		5 (3.2)		1 (1.3)		2 (2.6)		3 (1.9)	
Lack of Compliance	0 (0.0)		0 (0.0)		0 (0.0)		1 (1.3)		1 (1.3)		2 (1.3)	
Total Withdrawn	31 (40.3)		9 (11.7)		40 (26.0)		7 (9.1)		14 (18.2)		21 (13.6)	
Completed	46 (59.7)		68 (88.3)		114 (74.0)		28[c] (36.4)		44[c] (57.1)		72 (46.8)	

NA = Not applicable

[a] All percentages are based on the original 77 patients randomized to each treatment group

[b] Entry into the study extension was voluntary.

[c] One additional patient in each treatment group completed 96 weeks of therapy but did not complete the study. Because of this, these numbers do not correspond to the number of patients completing 96 weeks of therapy shown on Table 2.

Study 042

TABLE 13. Mean Primary Glycemic Parameters at Weeks 24, 48, 72, and 96 for Patients Completing the Extension

	Troglitazone N = 27	Glyburide N = 44
Fasting Serum Glucose, mg/dL		
Baseline Mean (SD)	236.4 (73.6)	256.8 (70.4)
Mean (SD) Change From Baseline at Week 24	-62.0 (73.8)	-67.8 (74.8)
Mean (SD) Change From Baseline at Week 48[a]	-55.7 (65.2)	-50.8 (82.3)
Mean (SD) Change From Baseline at Week 72[b]	-54.7 (77.1)	-43.9 (69.7)
Mean (SD) Change From Baseline at Week 96	-59.7 (71.6)	-42.6 (71.9)
Hemoglobin A_{1C}, %		
Baseline Mean (SD)	8.9 (1.6)	9.1 (1.5)
Mean (SD) Change From Baseline at Week 24	-0.8 (1.5)	-0.6 (1.2)
Mean (SD) Change From Baseline at Week 48[a]	-1.0 (1.7)	-0.3 (1.5)
Mean (SD) Change From Baseline at Week 72[b]	-1.0 (1.8)	-0.1 (1.8)
Mean (SD) Change From Baseline at Week 96	-1.0 (1.8)	-0.3 (1.6)
C-Peptide, ng/mL		
Baseline Mean (SD)	2.9 (1.4)	2.8 (1.1)
Mean (SD) Change From Baseline at Week 24[c]	-0.6 (0.9)	0.3 (1.2)
Mean (SD) Change From Baseline at Week 48[d]	-0.7 (1.1)	0.0 (1.1)
Mean (SD) Change From Baseline at Week 72[b]	-0.5 (1.6)	-0.3 (1.0)
Mean (SD) Change From Baseline at Week 96	-0.7 (1.2)	-0.1 (0.9)
Total Insulin, μIU/mL		
Baseline Mean (SD)	19.6 (18.6)	15.5 (12.7)
Mean (SD) Change From Baseline at Week 24[c]	-8.5 (12.7)	1.8 (13.4)
Mean (SD) Change From Baseline at Week 48[a]	-4.7 (14.7)	5.2 (14.3)
Mean (SD) Change From Baseline at Week 72[b]	-6.3 (15.7)	0.6 (11.0)
Mean (SD) Change From Baseline at Week 96	-6.8 (15.9)	2.2 (9.8)

[a] N = 27 for troglitazone and 37 for glyburide.
[b] N = 26 for troglitazone and 40 for glyburide.
[c] N = 27 for troglitazone and 42 for glyburide.
[d] N = 27 for troglitazone and 38 for glyburide.

study 042

TABLE 4. Mean Primary Cardiac Parameters at Weeks 24, 48, 72, and 96 for Patients Completing the Extension[a]

	Troglitazone N = 22	Glyburide N = 36
Left Ventricular Mass Index, g/m^2		
Baseline Mean (SD)	80.0 (10.2)	78.8 (10.2)
Mean (SD) Change From Baseline at Week 24	-0.3 (3.8)	-1.3 (4.2)
Mean (SD) Change From Baseline at Week 48[b]	-0.4 (5.3)	-3.4 (4.9)
Mean (SD) Change From Baseline at Week 72[c]	-1.7 (5.8)	-3.6 (6.8)
Mean (SD) Change From Baseline at Week 96	-1.8 (6.8)	-6.2 (9.9)
Confidence Interval[d]	(-4.2, 0.7)	(-9.0, -3.4)
Cardiac Index, L/min/m^2		
Baseline Mean (SD)	2.4 (0.4)	2.3 (0.3)
Mean (SD) Change From Baseline at Week 24	0.3 (0.4)	-0.1 (0.3)
Mean (SD) Change From Baseline at Week 48[b]	0.3 (0.4)	0.1 (0.5)
Mean (SD) Change From Baseline at Week 72[c]	0.3 (0.5)	0.2 (0.4)
Mean (SD) Change From Baseline at Week 96	0.3 (0.5)	-0.1 (0.4)
Confidence Interval[d]	(0.1, 0.5)	(-0.2, 0.0)
Stroke Volume Index, mL/m^2		
Baseline Mean (SD)	33.3 (5.2)	33.7 (4.9)
Mean (SD) Change From Baseline at Week 24	4.3 (3.6)	-0.9 (4.2)
Mean (SD) Change From Baseline at Week 48[b]	1.9 (4.3)	0.0 (4.7)
Mean (SD) Change From Baseline at Week 72[c]	4.9 (4.9)	1.0 (5.1)
Mean (SD) Change From Baseline at Week 96	4.6 (4.9)	-1.6 (4.4)
Confidence Interval[d]	(2.7, 6.4)	(-2.9, -0.4)

[a] Centers 2 through 5
[b] N = 22 for troglitazone and 33 for glyburide.
[c] N = 21 for troglitazone and 30 for glyburide.
[d] 90% confidence interval for mean change from baseline at Week 96

	Troglitazone N = 22	Glyburide N = 36
Peripheral Resistance[b], todd		
Baseline Mean (SD)	42.6 (7.5)	43.5 (7.4)
Mean (SD) Change From Baseline at Week 24	-5.6 (5.8)	2.2 (8.2)
Mean (SD) Change From Baseline at Week 48[c]	-5.0 (7.5)	-0.5 (8.6)
Mean (SD) Change From Baseline at Week 72[d]	-6.3 (9.4)	-2.3 (8.3)
Mean (SD) Change From Baseline at Week 96	-6.2 (7.7)	2.6 (7.1)
Mean Arterial Blood Pressure, mm Hg		
Baseline Mean (SD)	98.3 (8.8)	94.7 (6.4)
Mean (SD) Change From Baseline at Week 24	-2.0 (6.6)	0.5 (8.1)
Mean (SD) Change From Baseline at Week 48[c]	-1.5 (9.1)	1.6 (8.8)
Mean (SD) Change From Baseline at Week 72[d]	-4.9 (11.3)	2.2 (10.0)
Mean (SD) Change From Baseline at Week 96	-2.9 (10.3)	0.8 (8.9)

Adverse Events:

Although no deleterious effects of troglitazone were observed by echocardiography, 13% of patients on troglitazone reported cardiovascular AE's compared to 6% on glyburide. In addition, 14% of patients on troglitazone reported a peripheral edema compared to 9% on glyburide. 12 patients (16%) on troglitazone withdrew because of AE . Seven events were considered to be related to treatment - peripheral edema, allergic reaction, vasculitis, hemolytic-uremic syndrome. Depression, unsteady gait, increased CPK, and rash were also reported in troglitazone patients who withdrew but were not considered treatment-related. 9 patients 12%) on glyburide withdrew because of AE's. Of these, only three cases of hypoglycemia were considered likely to be drug-related.

Consultation from Division of Cardio-Renal Drug Products.

Dr Rodin of cardiorenal reviewed data from this study. In his consultation of April 1, 1997, he concluded that the study was adequate from a technical point of view and that the Sponsor was justified in excluding data from one of the centers becasue of flaws in data collection. Dr Lipicki, in his consultation of April 11, 1997 pointed out that imprecision of echocardiology is such that clinically significant changes could easily have been missed and that the only justifable conclusion is that " no disaster or no large improvement was present." As discussed in more detail below, a case by case comparison of the raw data from the local lab and the central lab, confirms Dr Lipicki's observation.

SAFETY ISSUES:

Cardiac effects -

As discussed in detail previously by Dr Fleming, the increased heart size observed in animal studies could result from expansion of vascular volume, direct cardiotoxicity or both. The only new information in the sNDA is data on levels of atrial natriuretic peptide (ANP) after three months of troglitazone. Like the fall in hematocrit regularly observed with troglitazone, an increase in ANP could be an indirect consequence of an increase in plasma volume. However, a change in ANP could also be due to a direct effect on the atria, a mechanism which would be consistent with the animal findings of karyopathy of the atrial myocytes. As shown in the table below, there is no consistent change in ANP with troglitazone treatment. The is very large variability among patients. The mean and median changes are small in comparison to the baseline levels. Therefore, I think these changes in ANP are not likely to be of importance.

Atrial Natriuretic Peptide, pg/ml after 3 months Troglitazone

	placebo	200	400	600	800
mean baseline	46	54	49	53	47
SD	31	79	51	73	60
final mean	56	55	60	54	55
change mean	10	0.77	11	1.2	7.6
SD	84	83	86	83	61
median	0.7	4.7	4.1	5.35	6.6

A preliminary report from Dr Tom Ju of DSI concerning echocardiography conducted in study 042 disclosed that echo data obtained at the local sites gave consistently higher values than from the central site. For this reason we requested that PD resubmit the echo data on a per site basis comparing the different data sets. Review of these data failed to show anything more than random variation. There were several cases at each site where there were large discrepencies between the readings from

the central lab and readings from the local site. These discrepencies occured equally in troglitazone and glyburide patients and were as likely to show increasing cardiac size as decreasing cardiac size. Reanalysis using the data from the local site would not have lead to a different conclusion about cardiac effects of troglitazone relative to that of glyburide. Review of the individual data has confirmed the correctness of Dr Lipicki's consultation that the intrinsic variability of the measurement is so large that only a "disaster" could have been detected.

Spontaneous Reports:

Since the marketing of troglitazone there have also been spontaneous reports that may be worthy of note. One 81 year old patient (970063) with underlying congestive heart failure died of increased congestive heart failure about five days after having been started on troglitazone. An additional patient (970109) developed a myocardial infarction and heart failure soon after starting troglitazone but the MD felt the drug was not the cause. However, a further patient developed leg edema, leukopenia, and anemia (970002) which the MD did attribute to troglitazone. There are also five cases of "lower extremity paresis" (970115 - 970120), all reported by a

Safety update

A safety update was submitted May 23 1997, which included reports of deaths and adverse events through February 1, 1997. The cumulative exposure to troglitazone in Parke-Davis studies is 1864 patient years. 2519 patients have received troglitazone, 868 for 12 months or longer. A total of 11 patients have died, 4 during the period of safety update (October 2, 1996 - March 1 1997). None of these deaths was felt to be related to troglitazone and there is no information in the detailed clinical summaries which suggest that the drug was implicated. There were also six patients in whom treatment was withdrawn because of an adverse event. Four of these were due to increases in liver enzymes, one due to anemia and one due to angioedema. That troglitazone therapy is associated with development of abnormal liver function tests and fall in hemogram is already in the current label. The report of angioedema is new. The patient developed symptoms on day 400 of 600 mg. Symptoms increased until day 411 when troglitazone was discontinued. Symptoms resolved by day 425. Although there was no rechallenge, the investigator concluded that the event was probably drug-related.

In summary, this safety update provides no new information which would require a change in labeling.

LABELING ISSUES:

According to the present labeling, Rezulin is indicated for type 2 diabetics inadequately controlled (Hbalc of 8.5%) despite multiple doses of insulin with the total dose exceeding 30 units/day. The proposed labeling would extend the indication to ALL type 2 diabetic patients who require pharmacological treatment and would allow the combined use of troglitazone with sulfonylureas or insulin. Each of these indications is discussed separately.

Monotherapy

Most of the patients in the monotherapy trials had previously been on other antidiabetic medications. Withdrawal of that medication lead to deterioration of glycemic control which was only partially reversed by troglitazone. No data are presented that patients did better on troglitazone than on their previous medication. Indeed, the studies consistently show that patients did worse on troglitazone than on the previous therapy. Data from these patients cannot be used as a basis for approval of troglitazone monotherapy. If the monotherapy indication were to be approved, the label would have to make it clear that troglitazone may be added to a sulfonylurea but not substituted for one.

Data on the use of troglitazone in previously untreated patients is sparse. The 6 month, pivotal study 032, shows efficacy only at 600 mg and only in 15 patients.

placebo	100mg	200mg	400mg	600mg
n= 18	16	18	19	15
A1c = 8.7	9.2	8.3	8.5	8.6
Rx effect	-0.08	-.65	-0.06	-1.35*

* $p<0.05$

These results alone cannot form the basis of approval of troglitazone for monotherapy. However, the Sponsor submitted two additional studies which are relevant to the monotherapy indication. In study 057, 20 of 46 previously untreated patients

(45%) responded to 6 weeks of 200 mg troglitizone based on FSG criteria and experienced a fall of HbAlc of 0.90% and 2.09% after 20 weeks of 200 mg and 400 mg respectively. As was the case with study 032, the numbers here are too small to provide a basis for approval. However, additional patients are provided in study 031. Unlike 032, and 057, this study lasted only 12 weeks, but the numbers of patients involved are substantially greater than the longer studies.

placebo	200mg	400mg	600mg	800mg
n=19	23	20	33	18
Alc, 8.3	8.4%	8.2%	8.5%	9.0%
Rx effect	-0.58	-0.50	-0.69	-0.78

As shown above, troglitazone appears to lower HbAlc about 0.6% relative to placebo, although no clear dose-response effect is seen. Combining all doses, this study provides data on 94 previously untreated patients in which troglitazone was effective as monotherapy. The 800 mg dose exceeds that in the label but is probably equivalent to 600 mg in the current formulation.

In order to be approved for monotherapy, the label should show one table in which the data from studies 031 and 032 are both shown. This would provide the physician with two important pieces of information: First, that the mean improvement in HbAlc is only about 0.7% which is roughly the same as what he might see with acarbose and less than what he might expect with metformin or a sulfonylurea. Second, that the dose-response relationship is different in the two studies and therefore not clearly established. In addition, reference must be made to the fact that the response rate is only about 50% in previously untreated patients as measured by a fall in FSG by 30 mg/dl. If patients fail to respond to 400 mg after 6 weeks, troglitazone treatment should be discontinued in favor of some other form of treatment.

Combined Therapy with a Sulfonylurea:

This is the stongest part of the application. The data show that the combination of troglitazone with a sulfonylurea is extremely effective, and gives much better results than with either agent alone. The only deficiency in the application is that there is only one pivotal study. Since this was a large multi center

study, we could ask the Sponsor to do a center by center analysis. DSI is auditing the data from the two largest centers, Indianapolis and Tampa. If data from each of these centers are consistent, and support the major conclusions, I think the requirement for a second study can be waived.

Combined Therapy with Insulin:

In the present label, troglitazone is indicated for patients in poor control (HbA1c 8.5%) despite multiple doses of insulin in excess of 30 units per day. The sNDA does not provide any new data on the use of troglitazone in insulin-treated patients. However, the proposed label states " Rezulin may be used concomitantly with (a sulfonylurea or) insulin to improve glycemic control". The proposed label therefore extends the indication to a class of patients (any type 2 patient on insulin) which has never been studied. PD does not provide any justification for this new indication. On their behalf, one might argue that it would appear inconsistent to allow the use of troglitazone in patients with mild diabetes (those needing monotherapy) and also in patients with severe diabetes (clinically unmanageable insulin resistance) but not allow the use of troglitazone in patients with moderate diabetes, such as those in reasonable control on ordinary doses of insulin. This argument assumes, however, that troglitazone monotherapy is approvable. Given the paucity of data submitted for this indication, major changes about the use of troglitazine as monotherapy will need made in the label in order for this assumption to be justified.

Adverse Effects of Heart Function:

PD is implementing a phase 4 protocol to examine the effects of troglitazone in patients with class 111 and class 1V heart failure. This protocol compares troglitazone with placebo as add-on therapy for six months to patients on sulfonylureas or insulin. The study is scheduled to begin June 1997 and be completed December 1998 and should provide the information to determine whether troglitazone can be used safely in these patients. In the meanwhile, extension of the indication to a much larger group of patients than in the original NDA requires that the admonition against the use of troglitazone in patients with heart failure be strengthened. Specifically, the statement

" ..caution is advised during the administration of Rezulin ...."

should be changed to:

" Rezulin should not be administered to patients with NYHA class 111 and 1V cardiac status unless the benefit of improved glycemic control is weighed against the potential risk of worsening the heart failure "

The primary purpose of this statement is to prevent the use of troglitazone as monotherapy where other treatment may be more appropriate. Given that monotherapy with troglitazone is probably less effective than monotherpy with metformin or glyburide, one would expect that those drugs would be preferred in most situations. A major exception would be in elderly patients with renal insufficiency in whom metformin is contraindicated because of lactic acidosis and glyburide is hazardous because of hypoglycemia. Troglitazone would appear to be a good choice in this situation except if the patient also has class 111 or 1V heart failure. That troglitazone should not be used in this setting should be clearly stated.

Renal Insufficiency:

The kidney does not appear to contribute to the metabolism of troglitazone so that adjustment of dosing due to renal insufficiency does not appear to be necessary. Although there are single dose PK data in patients with renal insufficiency, I am not aware of any clinical data. As written, the package insert could easily be interpreted to mean that troglitazone can be used safely in patients with frank renal failure and perhaps even in patients on dialysis. This needs to be changed. Whatever clinical data exist about the use of troglitazone in patients with renal insufficiency should be included. Otherwise, lack of experience should be acknowledged with an appropriately cautionary statement about the use of troglitazone in these situations.

Change in body weight:

Increases in body weight relative to placebo has been observed consistently to be associated with improved glycemic control due to troglitazone. This is not surprising. Insulin itself and sulfonylureas tend to increase body weight. As an insulin sensitizer, troglitazone would be expected to do the same. However, the proposed label does not give any data with respect to changes in body weight in patients taking troglitazone. This is not acceptable, because body weight is one of the parameters which physicians routinely measure in diabetes treatment

regimens.

Action Taken:

A draft of the preceeding section " labeling issues" was faxed to the Sponsor to give them the opportunity to revise the proposed label in a manner that would be acceptable. The revised label, faxed to us on June 2 and 3 makes the following changes and acknoweldgments:

1 Weight gain is acknowledged to be associated with the improved glycemic control achieved with troglitazone when added to glyburide.

2 Tables are included showing the response to troglitazone monotherapy in patients previously on diet alone. The text states that troglitazone monotherapy did not improve glycemic control in patients previously on a SFU.

3 Monotherapy should be started at 600 mg and discontinued in favor of an alternative treatment after 6-8 weeks if the response is inadequate.

4 Patients well controlled on a SFU should not be switched to troglitazone. In patients poorly controlled on an SFU, troglitazone should be added while continuing the SFU.

5 The statement is included that patients with class 3 and 4 heart failure should not receive troglitazone unless the expected benefits are thought to outweight the risk of worsening the CHF

6 Limited experience of troglitazone in renal failure is

acknowledged.

Summary and Recommendations

Current labeling limits the use of troglitazone to type 2 diabetics on insulin with clinically unmanageable insulin resistance. The data presented in this sNDA provide a firm basis for extending its use to patients inadequately controlled on sulfonylureas. Addition of troglitazone to a sulfonylurea is likely to be as effective as metformin, and certainly more effective than addition of acarbose or miglitol. Furthermore, troglitazone does not have the gastrointestinal side effects of these other medications, and is not contraindicated in the presence of renal insufficiency as is metformin. Extension of the labeling to include monotherapy with troglitazone is more problematic.

As discussed in detail already, most of the data on troglitazone monotherapy in this sNDA were from patients who had previously been on a sulfonylurea. Although troglitazone was better than placebo, it was usually less effective than the sulfonylurea which had been discontinued. In their most recent revision to the proposed label, PD acknowledges that troglitazone monotherapy should not be used in place of sulfonylurea monotherapy, but retains the indication for patients inadequately treated with diet alone. The data supporting this indication are not compelling. That the recommended starting dose for monotherapy is 600 mg (which is also the maximum recommended dose) is an acknowledgment that the 400 mg dose was ineffective in their one 26 week study. The statement that troglitazone should be discontinued after 6-8 weeks if ineffective is also an acknowledgment that a large number of patients are not expected to respond. To the best of my knowledge, no other antidiabetic agent currently marketed has a similar admonition in its label.

The difference in results between 400 mg and 600 mg in study 032 probably is due to the small number of patients studied. I believe we would be justified to not approve the monotherapy indication until PD has done a 26 week study with an adequate number of patients. On the other hand, I believe we must recognize that failure to approve the monotherapy indication at this time would be likely to have certain undesirable consequences.

Given its effectivness in combination with sulfonylureas, it is likely that troglitazone will soon be used widely. In the absence of appropriate labeling information, physicians will probably begin to prescribe troglitazone as monotherapy in the same way they prescribe it in combination with sulfonylureas. This would be a mistake because the required dose is higher and the likely treatment effect is less. Physicians are presently able to prescribe metformin, miglitol and acarbose in the same way as monotherapy or in combination with a SFU. But having not been given labeling information to the contrary, how would they know that the situation with troglitazone is different?

It would not be easy for PD to do a large 26 week trial of troglitazone versus placebo in previously untreated patients. Some would argue that it is unethical to keep patients on placebo for so long while safe and effective treatments are readily available. At the very least, it would be difficult to do such a study and we do not want to take any action which would force PD to seek out investigators who are willing to leave patients untreated (or even worse, to take them off of sulfonylureas) in order to make them eligible to participate in a study. Furthermore, there is little doubt that such a study would give positive results. The effects of troglitazone increase over time. Troglitazone showed modest efficacy (about 0.6 - 0.8 % fall in HbA1c) at 200-600 mg in an adequately powered 12 week study, and it is likely that similar results would be obtained if the study were repeated for 26 weeks. Perhaps such a study would give us more definitive dose-response information than we have now, but this is by no means certain. Given the fact that some patients respond well while others fail to respond at all, the mean efficacy is modest and a few outliers can have a large effect.

Given all these considerations, I recommend that we accept the monotherapy indication. The revised labeling provides the physician with all the relevant information currently available, and permits him to make an informed choice about troglitazone monotherpy.

Robert I Misbin MD
Medical Officer
HFD 510
June 3,1997
cc/nda 20-720 misbin/fleming/sobel/johnstonM/

excellent review
see note

1/4/97

NDA 20-720/S-002 & S-003
Rezulin™ 200 mg & 400 mg tablets

For Safety Update Review, See Page 27 of the Medical Officers Review

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-720/20-719 (S-002 and S-003)

JUL 28 1997

SPONSOR: Parke-Davis

NAME OF DRUG: Rezulin™/Prelay™ (troglitazone) Tablets

INDICATION: Treatment of Type II Diabetes
- Monotherapy (S-003)
- Combination with sulfonylureas (S-002)

DOCUMENTS REVIEWED: Vol. 1, 27-45 dated February 3, 1997
Vol. 1 dated February 14, 1997

MEDICAL REVIEWER: Robert Misbin, MD (HFD-510).

I. Background

Two major controlled studies (Study 991-032 and 991-055) were conducted in Type II diabetes patients not treated with insulin. Study 991-032 was conducted in patients currently uncontrolled by diet/exercise or with less than or equal to half-maximal doses of a sulfonylurea with the objective of glycemic control. This placebo-controlled study examined 100, 200, 400 and 600 mg troglitazone monotherapy for 6 months in parallel groups. Study 991-055 assessed the effect of troglitazone as add-on therapy in combination with a sulfonylurea and was conducted in patients who had failed oral sulfonylurea therapy. Troglitazone was tested as monotherapy (200, 400 and 600 mg) and as combination therapy of troglitazone (200, 400 and 600 mg) with 12 mg (6 mg twice daily) of micronized glyburide versus 12 mg of micronized glyburide monotherapy as the control for 1 year after an initial 4-week baseline phase during which all patients received 12 mg of micronized glyburide therapy daily.

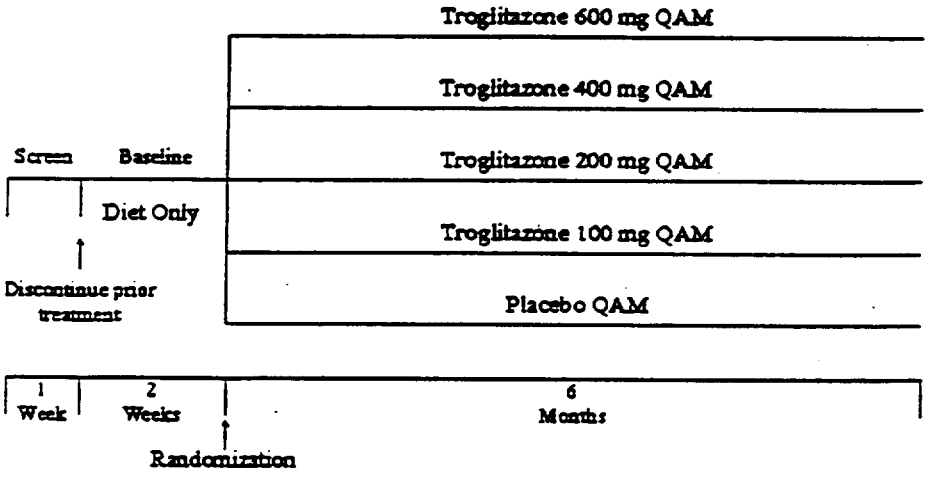
For both studies, the primary efficacy endpoints were hemoglobin A_{1c} (HbA_{1c}) and fasting serum glucose (FSG). In Study 991-032, determination of efficacy was based on change from baseline for each troglitazone group compared with placebo using analysis of covariance (ANCOVA) step-down tests for linear trend and 95% confidence interval via Dunnett's test. Being a placebo-controlled study, this reviewer relied more on ANCOVA p-values. In Study 991-055, determination of efficacy was based on change from baseline for each troglitazone monotherapy group compared with glyburide (active control) and troglitazone/glyburide combination therapy group compared with glyburide (active control) using analysis of covariance (ANCOVA) step-down tests for linear trend and 95% confidence intervals via Dunnett's test. Being an active-

controlled study, this reviewer relied more on 95% confidence intervals via Dunnett's test. The intent-to-treat (ITT) patient sample, using last observation carried forward (LOCF) for patients terminating from the study early, was the primary sample for assessing efficacy. The baseline was used as a covariate.

Please note that 95% confidence intervals via Dunnett's test are not standard confidence intervals. These are based on the recommendations of Hochberg and Tamhane (1987)[1] and they adjust for the multiple comparisons.

II. Study 991-032

This placebo-controlled study examined 100, 200, 400 and 600 mg troglitazone monotherapy for 6 months in parallel groups in patients with NIDDM whose HbA_{1c} was > 6.5, FSG was > 140 mg/dl and C-peptide was $\geq$ 1.5 ng/ml. There was a 2-week baseline(washout) period from previous therapy with less than or equal to half-maximal doses of a sulfonylurea. The Study Design is provided below.



There were 24 centers that participated in this study. Due to small sample sizes per group per center, centerwise analysis was not done.

Statistical Reviewer's Review, Analysis and Efficacy Results:

The primary efficacy variables were change from baseline in FSG and HbA_{1c} after 6 months of treatment (LOCF).

[1] Yosef Hochberg and Ajit Tamhane (1987): *Multiple Comparison Procedures*, John Wiley & Sons, New York.

Summary statistics for baseline and change from baseline at each month of the double-blind treatment period were provided for each efficacy variable by the sponsor. Baseline was defined as the last available measurement taken within weeks -2, -1 and 0. Change from baseline at month 6 was calculated as the Month 6 measurement minus the baseline.

Baseline characteristics of all patients were computed and they match with the sponsor's results. The sponsor summarized these results in Table 4 (pages 20-21, vol. 36). Sponsor's Table 4 is included in the Appendix (pages 11-12 of this review).

Patients were evenly distributed across treatment groups with respect to sex, race, age, duration of diabetes, BMI, FSG, HbA_{1c}, and C-peptide.

The sponsor stated that two-hundred eighty six patients (71%) completed the study. The sponsor provided details of patient disposition in Table 6 (page 24, vol. 36). Sponsor's Table 6 is included in the Appendix (page 13 of this review).

The number of patients included in the primary efficacy analyses is summarized in the following Table.

NUMBER OF PATIENTS	TMNTS					TOTAL
	Placebo	Trog 100	Trog 200	Trog 400	Trog 600	
Number of Randomized Patients	80	81	83	78	80	402
Number of Patients in ITT Analysis	78	78	81	76	79	392
Number of Patients in Completer's Analysis	49	49	58	59	62	277

Please note that the number of patients included in the completers' analysis is 277 and not 286. The sponsor did not provide any explanation for this obvious discrepancy.

The following Table summarizes statistical reviewer's results of primary efficacy analyses (ITT) for change from baseline at month 6 for HbA_{1c} and FSG. As stated earlier, being a placebo-controlled study, this reviewer relied more on ANCOVA p-values in interpreting the results.

The difference from placebo in HbA_{1c} at month 6 was -0.65% for patients treated with 400 mg troglitazone and -1.08% for patients treated with 600 mg troglitazone. FSG decreased significantly at month 6 compared with placebo by -42.41, -51.35 and -59.66 mg/dL at 200, 400 and 600 mg troglitazone, respectively.

Assumptions of the ANCOVA model for change from baseline were verified by examining residuals from the model.

	Placebo	Trog 100	Trog 200	Trog 400	Trog 600
HbA_{1c}					
N	78	78	81	76	79
Mean Baseline (SD)	8.73 (1.71)	8.58(1.71)	8.63(1.71)	8.63(1.82)	8.88(1.70)
Adj. Mean Chg. From Baseline (SE)	1.46(0.21)	1.57(0.21)	1.10(0.21)	0.81(0.22)	0.38(0.21)
Difference from Placebo (SE)	-	0.11(0.30)	-0.36(0.29)	-0.65(0.30)	-1.08(0.30)
95% CI of difference (Dunnett's Test)	-	(-0.62,0.84)	(-1.08,0.36)	(-1.38,-0.08)	(-1.81,-0.36)
P-Value for Step-Down Test	-	0.7103	0.2238	0.0505	0.0003
FSG					
N	79	77	81	76	79
Mean Baseline (SD)	224 ((65)	234 (62)	240 (70)	229 (74)	240 (68)
Adj. Mean Chg. From Baseline (SE)	23.95(6.71)	12.60(6.80)	-18.47(6.62)	-27.40(6.85)	-35.71(6.73)
Difference from Placebo (SE)	-	-11.35(9.45)	-42.41(9.34)	-51.35(9.47)	-59.66(9.39)
95% CI of difference (Dunnett's Test)	-	(-34.5,11.8)	(-65.3,-19.5)	(-74.6,-28.1)	(-82.7,-36.6)
P-Value for Step-Down Test	-	0.2306	0.0001	0.0001	0.0001

Sponsor's Additional Analyses:

Because the mean FSG levels increased significantly ($p \leq 0.01$) from screening to baseline (see Figure on page 14 of this review) for those patients who had received prestudy oral antidiabetic therapy, regardless of treatment groups, efficacy analyses were conducted by the sponsor for the following two subpopulations: (1) patients treated with diet therapy alone prestudy, and (2) patients treated with oral antidiabetic therapy prestudy. Sponsor's Table 10 (page 33, vol. 36) provides the results of both analyses and is included in the Appendix (page 15 of this review). This Table provides p-values based on the ANCOVA step-down test for linear as well as 95% confidence interval (CI) based on Dunnett's test. Some of these CIs do not agree with the p-values because of the obvious difference in the two methods. As stated earlier, being a placebo-controlled study, this reviewer relied more on ANCOVA p-values in interpreting the results.

These results show that there is some evidence (based on only 15 patients) that troglitazone is effective in improving glycemic control over a 6-month period at a dose of 600 mg in patients with NIDDM previously treated with diet therapy alone. Patients treated with antidiabetic therapy prestudy showed significantly greater reductions in FSG and HbA_{1c} compared with placebo at the 400 and 600 mg dose of troglitazone. Graphical results for FSG and HbA_{1c} are provided on pages 16-17 of this review.

The sponsor has also provided a "responder analysis" where a patient is defined to be a responder if reduction from baseline in HbA_{1c} is ≥ 1% or reduction in FSG is ≥ 30 mg/dL. However, the responder analysis is based on change from baseline after the deterioration in glycemic control resulting from the two-week washout. According to the Medical Reviewer, this approach is misleading (see Medical Reviewer's Review) as it conceals the likely possibility that these patients would have done better had they been left on the sulfonylurea.

Completers' Analysis:

The ITT population included 392 patients (of 402 randomized) and the analysis of completers included 277 patients (of 286 completers). The sponsor did not explain this obvious discrepancy. However, completers' results were similar to those of ITT results.

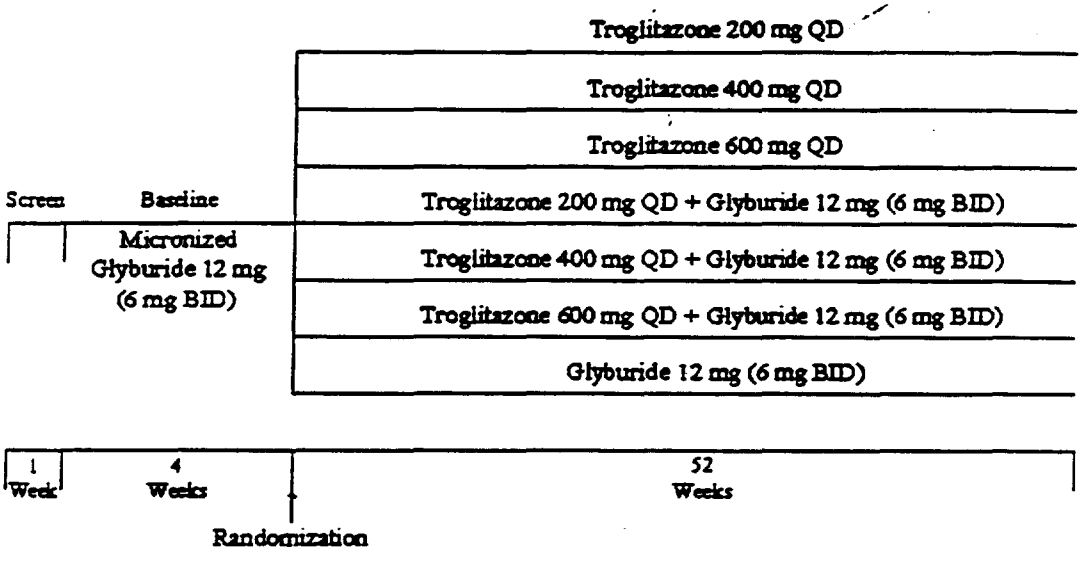
Conclusion:

There is statistically significant evidence that troglitazone 400 mg and 600 mg over a 6-month period are efficacious in comparison to placebo in improving glycemic control in patients with NIDDM.

There is some evidence that troglitazone monotherapy is effective in improving glycemic control over a 6-month period at a dose of 600 mg in patients with NIDDM previously treated with diet therapy alone. Patients treated with antidiabetic therapy prestudy showed significantly greater reductions in FSG and HbA_{1c} compared with placebo at the 400 and 600 mg doses of troglitazone.

III. Study 991-055

This was a 12-month, double-blind, randomized, parallel group, active control, multicenter study. After an initial screening visit, patients meeting the inclusion criteria entered a 4-week baseline phase (unblinded) in which they received 12 mg micronized glyburide (6 mg BID). At the end of the baseline phase, patients who still exhibited a fasting serum glucose (FSG) of > 140 mg/dL and < 300 mg/dL were randomized to 1 of 7 blinded parallel treatment arms. Treatment consisted of troglitazone monotherapy, troglitazone/glyburide combination therapy, or glyburide monotherapy (active control).



There were 30 centers that participated in this study. Due to small sample sizes per treatment arm per center, centerwise analysis was not done.

Statistical Reviewer's Review, Analysis and Efficacy Results:

The primary efficacy variables were change from baseline in FSG and HbA_{1c} after 12 months of treatment (LOCF). The comparison of these changes to active control (glyburide) was the primary measure of efficacy.

Summary statistics for baseline and change from baseline at each visit were provided for each efficacy variable by the sponsor. For each patient, the baseline measurement for a given variable was defined as the measurement at week 0. Change from baseline at month 12 was calculated as the Month 12 measurement minus the baseline.

Baseline characteristics of all patients were computed and they match with the sponsor's results. The sponsor summarized these results in Table 4 (pages 22-23, vol. 32). Sponsor's Table 4 is included in the Appendix (pages 18-19 of this review). Patients were evenly distributed across treatment groups with respect

to sex, race, age, duration of diabetes and BMI. The mean BMI of 32 mg/kg^2 indicates that, in general, the patients were obese at baseline. Overall, the mean duration of diabetes was greater than 8 years; mean FSG was 224 mg/dL and mean HbA_{1c} was 9.6%, indicating that these patients were generally in poor glycemic control at baseline.

The sponsor stated that three-hundred eighteen patients (58%) completed the study. The sponsor provided details of patient disposition in Table 6 (page 26, vol. 32) which is included in the Appendix (page 20 of this review). The number of patients included in the primary efficacy analyses at week 52 is given below.

Number of Patients	Troglitazone Monotherapy			Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg	400 mg	600 mg	200mg/12mg	400mg/12mg	600mg/12mg		
Randomized	78	81	78	78	76	82	79	552
ITT Analysis	78	78	76	78	76	80	79	545
Completers'	22	37	34	55	55	70	45	318

The following Table summarizes the statistical reviewer's results of primary efficacy analyses (ITT) for change from baseline at week 52 for HbA_{1c} and FSG for two comparisons: troglitazone monotherapy versus glyburide monotherapy (active control), and combination therapy (troglitazone/glyburide) versus glyburide (active control). Appropriate confidence intervals were computed.

Patients treated with 200mg/12mg, 400mg/12mg and 600mg/12mg troglitazone/glyburide combination therapy had adjusted mean changes from baseline in FSG of -31.0, -38.0 and -56.4 mg/dL respectively; these represent mean differences from glyburide of -53.7, -60.8 and -79.1 mg/dL respectively (all $p<0.0001$). Ninety-five percent confidence intervals show that the combination therapy is more efficacious than glyburide alone. Patients treated with 400mg and 600mg troglitazone monotherapy showed decreases in FSG compared with glyburide; however, these decreases were not significant. A similar pattern was observed for HbA_{1c}. Patients treated with 200mg/12mg, 400mg/12mg and 600mg/12mg combination therapy had mean changes from baseline of -0.70%, -0.91% and -1.75% respectively; these represent mean differences from glyburide in HbA_{1c} of -1.60%, -1.81% and -2.65% respectively (all $p<0.0001$). Ninety-five percent confidence intervals show that the combination therapy is more efficacious than glyburide alone. Graphical results for FSG and HbA_{1c} are provided on page 21 of this review.

Patients treated with troglitazone monotherapy had increases from baseline in HbA_{1c}. The mean HbA_{1c} was significantly higher for 200mg of troglitazone compared to glyburide. The sponsor explained it by stating that this may have been attributed to carrying forward data from the patients treated with 200mg troglitazone that withdrew from the study due to lack of efficacy (55% of patients in this treatment group withdrew due to lack of efficacy).

	Combination Therapy			Glyburide Monotherapy
	200mg/12mg	400mg/12mg	600mg/12mg	
FSG				
N	78	76	80	79
Mean Baseline (SD)	226(51)	231(43)	221(52)	222(41)
Adj. Mean Chg. from Baseline (SE)	-31.0(7.0)	-38.0(7.1)	-56.4(6.9)	22.7(6.9)
Adj. Mean Diff. from Glyburide (SE)	-53.7(9.7)	-60.8(9.7)	-79.1(9.6)	- -
95% CI for Diff. (Dunnett's Test)	(-78.63, -28.85)	(-85.83, -35.68)	(-103.87, -54.39)	
P-Value for Step-Down Test	< 0.0001	< 0.0001	< 0.0001	
HbA_{1c}				
N	78	76	80	79
Mean Baseline (SD)	9.49(1.32)	9.72(1.32)	9.45(1.51)	9.57(1.24)
Adj. Mean Chg. from Baseline (SE)	-0.70(0.20)	-0.91(0.20)	-1.75(0.20)	0.90(0.20)
Adj. Mean Diff. from Glyburide (SE)	-1.60(0.28)	-1.81(0.28)	-2.65(0.28)	
95% CI for Diff. (Dunnett's Test)	(-2.31, -0.88)	(-2.53, -1.10)	(-3.36, -1.94)	
P-Value for Step-Down Test	< 0.0001	< 0.0001	< 0.0001	
	Troglitazone Monotherapy			Glyburide Monotherapy
	200mg	400mg	600mg	
FSG				
N	78	78	76	79
Mean Baseline (SD)	226(45)	212(50)	230(49)	222(41)
Adj. Mean Chg. from Baseline (SE)	42.4(7.0)	20.6(7.0)	11.1(7.1)	22.7(6.9)
Adj. Mean Diff. from Glyburide (SE)	19.6(9.7)	-2.2(9.7)	-11.6(9.7)	
95% CI for Diff. (Dunnett's Test)	(-5.29, 44.55)	(-27.12, 22.76)	(-36.70, 13.42)	
P-Value for Step-Down Test	0.1818	0.9999	0.6891	
HbA_{1c}				
N	78	79	76	79
Mean Baseline (SD)	9.54(1.40)	9.44(1.44)	9.71(1.69)	9.57(1.24)
Adj. Mean Chg. from Baseline (SE)	1.92(0.20)	0.85(0.20)	0.93(0.20)	0.90(0.20)
Adj. Mean Diff. from Glyburide (SE)	1.02(0.28)	-0.05(0.28)	0.03(0.28)	
95% CI for Diff. (Dunnett's Test)	(0.31, 1.74)	(-0.76, 0.66)	(-0.69, 0.75)	
P-Value for Step-Down Test	0.0002	0.8638	0.9138	

Completers' Analysis:

This reviewer has performed the analysis of completers' sample and has found the results to be similar to those of ITT sample for combination therapy. But for monotherapy, results for completers' sample are different from those of ITT sample due to high dropout rate in patients taking troglitazone alone, primarily because of lack of efficacy.

Conclusion:

There is statistically significant evidence (based on 95% confidence intervals) that the combination therapy of troglitazone/glyburide in doses of 200mg/12mg to 600mg/12mg over a 12-month period is more efficacious than glyburide monotherapy in patients with NIDDM who are not adequately controlled on sulfonylurea therapy.

IV. Statistical Reviewer's Conclusions (That May Be Conveyed To The Sponsor)

Study 991-032

There is statistically significant evidence that troglitazone 400 mg and 600 mg over a 6-month period are efficacious in comparison to placebo in improving glycemic control in patients with NIDDM.

There is some evidence (based on only 15 patients) that troglitazone monotherapy is effective in improving glycemic control over a 6-month period at a dose of 600 mg in patients with NIDDM previously treated with diet therapy alone. Patients treated with antidiabetic therapy prestudy showed significantly greater reductions in FSG and HbA_{1c} compared with placebo at the 400 and 600 mg doses of troglitazone.

Study 991-055

There is statistically significant evidence (based on 95% confidence intervals) that the combination therapy of troglitazone/glyburide in doses of 200mg/12mg to 600mg/12mg over a 12-month period is more efficacious than glyburide monotherapy in patients with NIDDM who are not adequately controlled on sulfonylurea therapy.

BKTaneja

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Mathematical Statistician (Biomed)

Concur: Dr. Nevius SEN 7-28-97

Mr. Marticello Dennis Marticello

cc:
Archival NDA 20-720/20-719
HFD-510/Sobel, Troendle, Fleming, Misbin, Johnston
HFD-715/Nevius, Marticello, Taneja, Division File, Chron
✓ HFD-510
This review contains 21 pages: 9 pages of text and 12 pages of Appendix.

APPENDIX

TABLE 4. Patient Characteristics - All Patients
(Page 1 of 2)

	Placebo N = 80	Troglitazone (mg) 100 N = 81	200 N = 83	400 N = 78	600 N = 80	Total N = 402
Sex, N (%)						
Men	57 (71.3)	43 (53.1)	44 (53.0)	46 (59.0)	48 (60.0)	238 (59.2)
Women	23 (28.7)	38 (46.9)	39 (47.0)	32 (41.0)	32 (40.0)	164 (40.8)
Postmenopausal	14 (17.5)	25 (30.9)	19 (22.9)	27 (34.6)	21 (26.2)	106 (26.4)
Age, yr						
Mean (SD)	54 (10)	54 (12)	53 (10)	56 (11)	56 (10)	54 (11)
Median (Min, Max)	54 (34, 76)	53 (23, 86)	51 (34, 79)	58 (28, 77)	56 (35, 84)	55 (23, 86)
<65 Years, N (%)	67 (84)	65 (80)	72 (87)	60 (77)	63 (79)	327 (81)
≥65 Years, N (%)	13 (16)	16 (20)	11 (13)	18 (23)	17 (21)	75 (19)
Race, N (%)						
White/Caucasian	59 (73.8)	65 (80.2)	58 (69.9)	55 (70.5)	62 (77.5)	299 (74.4)
Black	11 (13.8)	8 (9.9)	9 (10.8)	4 (5.1)	8 (10.0)	40 (10.0)
Hispanic	6 (7.5)	7 (8.6)	13 (15.7)	12 (15.4)	7 (8.8)	45 (11.2)
Asian	2 (2.5)	1 (1.2)	2 (2.4)	4 (5.1)	1 (1.2)	10 (2.5)
Native American	1 (1.2)	0 (0)	0 (0)	1 (1.3)	2 (2.5)	4 (1.0)
Other	1 (1.2)	0 (0)	1 (1.2)	2 (2.6)	0 (0)	4 (1.0)
Body Mass Index (BMI), kg/m^2						
Mean (SD)	32.3 (6.7)	33.0 (7.1)	33.5 (8.1)	30.6 (5.0)	32.5 (5.3)	32.4 (6.6)
Median (Min, Max)	30.8	33.2	32.9	30.6	31.5	31.6
Duration of Diabetes, yr						
Mean (SD)	5.0 (5.1)	5.1 (5.7)	4.7 (5.3)	6.7 (6.0)	5.3 (5.6)	5.3 (5.6)
Median (Min, Max)	3.5	3.0	3.0	5.0	3.5	4.0

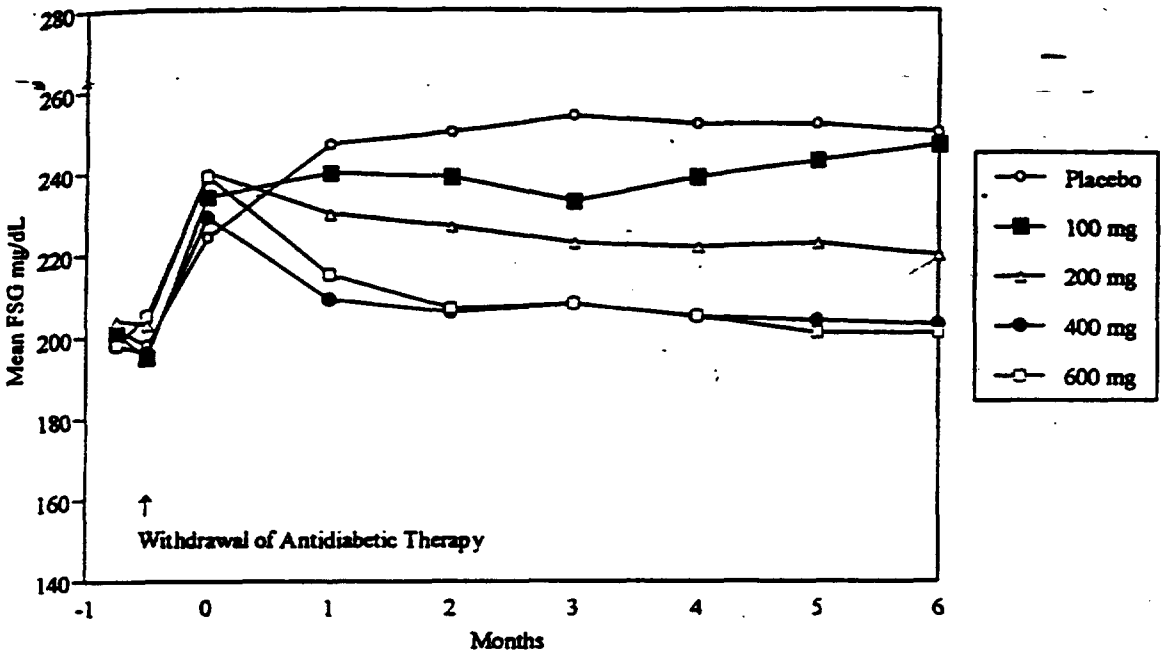
TABLE 4. Patient Characteristics - All Patients
(Page 2 of 2)

	Placebo N = 80	Troglitazone (mg) 100 N = 81	200 N = 83	400 N = 78	600 N = 80	Total N = 402
Baseline FSG, mg/dl.						
Mean (SD)	224 (65)	234 (62)	241 (70)	228 (74)	240 (67)	234 (68)
Median (Min, Max)	225	230	226	208	233	224
Baseline HbA_{1C}, %						
Mean (SD)	8.7 (1.7)	8.6 (1.7)	8.7 (1.7)	8.6 (1.8)	8.9 (1.7)	8.7 (1.7)
Median (Min, Max)	8.6	8.3	8.3	8.1	8.5	8.4
Baseline C-Peptide, ng/mL						
Mean (SD)	2.5 (0.9)	2.9 (1.6)	2.5 (0.9)	2.6 (1.0)	2.4 (1.0)	2.6 (1.1)
Median (Min, Max)	2.4	2.7	2.3	2.6	2.2	2.4

TABLE 6. Patient Disposition
[Number (%) of Patients]

	Placebo	Troglitazone (mg)				Total	
		100	200	400	600		
Randomized to Treatment	80	81	83	78	80	402	
Withdrawn Prior to End of Treatment							
Lack of Efficacy	21 (26.2)	17 (21.0)	16 (19.3)	10 (12.8)	10 (12.5)	74	(18.4)
Adverse Event	3 (3.8)	4 (4.9)	5 (6.0)	2 (2.6)	0 (0.0)	14	(3.5)
Lack of Compliance	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.3)	1 (1.2)	4	(1.0)
Other/Administrative	5 (6.3)	5 (6.2)	4 (4.8)	6 (7.7)	4 (5.0)	24	(6.0)
Total Withdrawn	30 (37.5)	27 (33.3)	25 (30.1)	19 (24.4)	15 (18.8)	116	(28.9)
Completed Study[a]	50 (62.5)	54 (66.7)	58 (69.9)	59 (75.6)	65 (81.3)	286	(71.1)

[a] Based on investigator's response on termination case report form



Mean FSG by Time, Including Screening and Baseline Values (ITT)

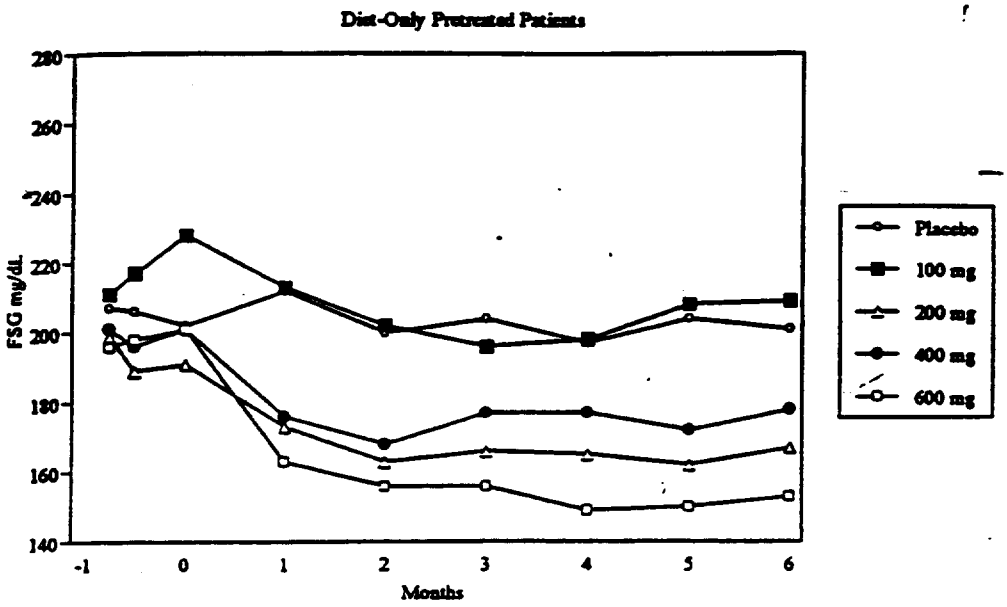
TABLE 10. Primary Efficacy Parameters at Month 6: Prestudy Therapy (Diet and Oral Therapy)

Prestudy Parameter Therapy	Placebo	Troglitazone (mg)			
		100	200	400	600
DIET ONLY					
HbA_{1C}					
N	18	16	18	19	15
Mean Baseline (SD)	8.7 (1.9)	9.2 (2.0)	8.3 (1.5)	8.5 (2.1)	8.6 (2.2)
Adjusted Mean Change (SE)	0.40 (0.40)	0.48 (0.41)	-0.24 (0.40)	0.34 (0.36)	-0.95 (0.42)
Difference From Placebo		0.08	-0.65	-0.06	-1.35*
95% CI of Difference[a]		(-1.31, 1.47)	(-2.10, 0.81)	(-1.37, 1.24)	(-2.79, 0.08)
Fasting Serum Glucose					
N	18	17	18	19	15
Mean Baseline (SD)	202 (68)	228 (66)	191 (53)	201 (61.1)	201 (56)
Adjusted Mean Change (SE)	-6.2 (14.1)	-6.9 (14.3)	-24.4 (14.2)	-16.6 (12.6)	-48.4 (14.9)
Difference From Placebo		-0.7	-18.2	-10.4	-42.2*
95% CI of Difference[a]		(-49.1, 47.7)	(-69.6, 33.1)	(-56.4, 35.6)	(-92.8, 8.4)
ORAL ANTIDIABETIC THERAPY					
HbA_{1C}					
N	60	62	63	57	64
Mean Baseline (SD)	8.8 (1.7)	8.4 (1.6)	8.7 (1.8)	8.7 (1.74)	8.9 (1.6)
Adjusted Mean Change (SE)	1.86 (0.24)	1.97 (0.24)	1.48 (0.24)	1.06 (0.25)	0.69 (0.24)
Difference From Placebo		0.11	-0.38	-0.80*	-1.17*
95% CI of Difference[a]		(-0.72, 0.94)	(-1.20, 0.44)	(-1.63, 0.04)	(-1.98, -0.35)
Fasting Serum Glucose					
N	61	60	63	57	64
Mean Baseline (SD)	231 (63)	235 (61)	254 (69)	239 (76)	249 (67)
Adjusted Mean Change (SE)	32.7 (7.8)	20.7 (7.9)	-15.7 (7.7)	-28.3 (8.0)	-33.1 (7.7)
Difference From Placebo		-12.0	-48.3*	-60.9*	-65.7*
95% CI of Difference[a]		(-38.8, 14.8)	(-74.8, -21.8)	(-87.8, -34.1)	(-92.0, -39.4)

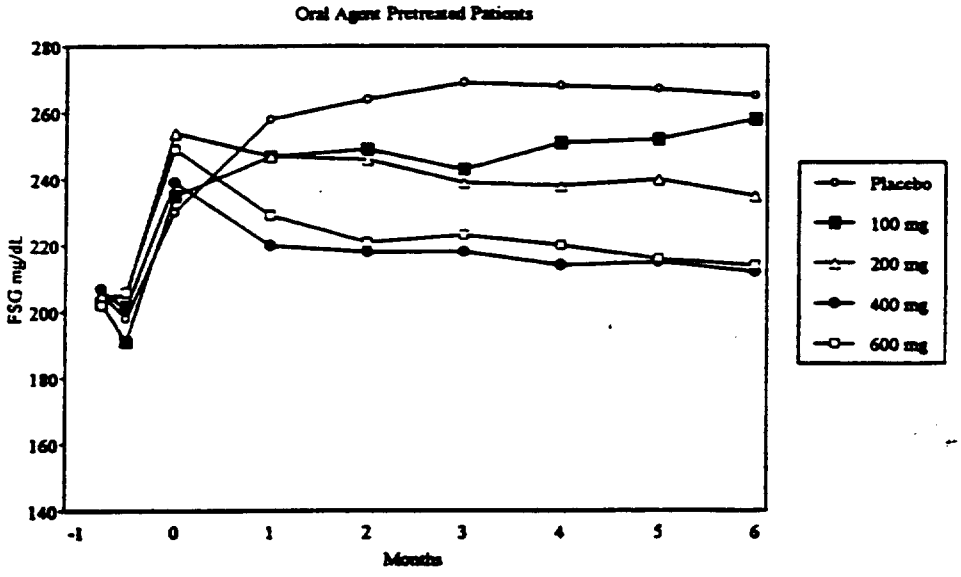
* $p \leq 0.05$, based on step-down test for linear trend.
[a] Via Dunnett's test

Study 991-032

a)

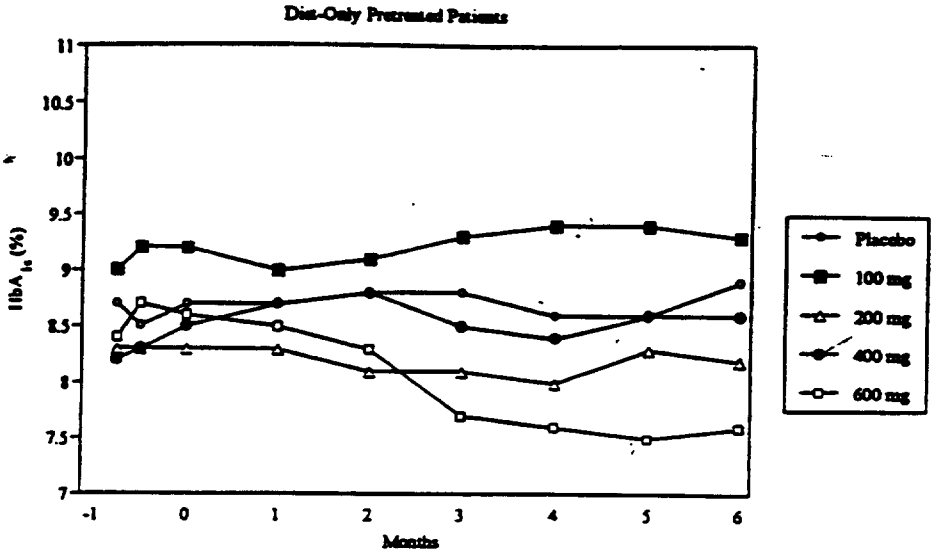


b)

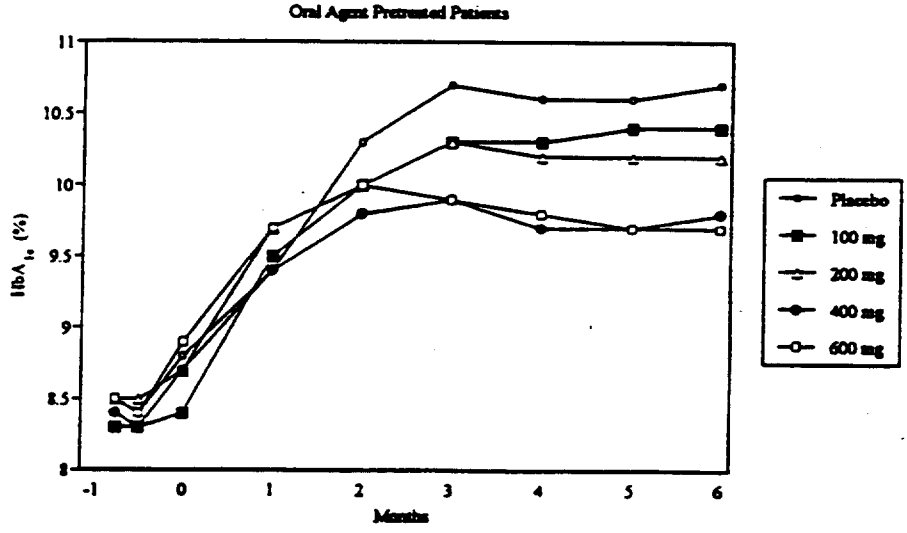


Mean FSG by Time and Prestudy Therapy

a)



b)



Mean HbA_{1c} by Time and Prestudy Therapy

TABLE 4. Patient Characteristics at Baseline - All Patients
(Page 1 of 2)

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Grand Total
	200 mg N = 78	400 mg N = 81	600 mg N = 78	200 mg/12 mg N = 78	400 mg/12 mg N = 76	600 mg/12 mg N = 82	N = 79	N = 552
Sex, N (%)								
Men	40 (51.3)	43 (53.1)	48 (61.5)	54 (69.2)	50 (65.8)	49 (59.8)	49 (62.0)	333 (60.3)
Women	38 (48.7)	38 (46.9)	30 (38.5)	24 (30.8)	26 (34.2)	33 (40.2)	30 (38.0)	219 (39.7)
Postmenopausal	29 (37.2)	31 (38.3)	22 (28.2)	19 (24.4)	17 (22.4)	22 (26.8)	27 (34.2)	167 (30.3)
Age, yr								
Mean (SD)	58.5 (10.4)	58.9 (10.6)	56.4 (10.2)	56.9 (10.4)	57.1 (10.2)	56.3 (11.6)	58.7 (10.8)	57.5 (10.6)
Median	60.5	61.0	58.5	56.0	57.5	56.5	59.0	58.0
Min, Max								
<65 years, N (%)	52 (66.7)	61 (75.3)	61 (78.2)	59 (75.6)	56 (73.7)	64 (78.0)	56 (70.9)	409 (74.1)
≥65 years, N (%)	26 (33.3)	20 (24.7)	17 (21.8)	19 (24.4)	20 (26.3)	18 (22.0)	23 (29.1)	143 (25.9)
Race, N (%)								
White/Caucasian	63 (80.8)	64 (79.0)	59 (75.6)	54 (69.2)	62 (81.6)	61 (74.4)	61 (77.2)	424 (76.8)
Black	5 (6.4)	6 (7.4)	4 (5.1)	11 (14.1)	4 (5.3)	5 (6.1)	5 (6.3)	40 (7.2)
Hispanic	10 (12.8)	11 (13.6)	11 (14.1)	12 (15.4)	9 (11.8)	14 (17.1)	12 (15.2)	79 (14.3)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)	1 (1.2)	0 (0.0)	3 (0.5)
Native American	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Other	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.3)	4 (0.7)
Duration of Diabetes, yr								
Mean (SD)	8.6 (5.7)	8.8 (7.8)	7.7 (5.5)	8.7 (6.1)	8.7 (5.9)	7.7 (6.1)	9.0 (8.4)	8.4 (6.6)
Median	8.0	7.0	6.0	7.0	7.0	5.5	7.0	7.0
Min, Max	<1, 27.0	<1, 40.0	1.0, 30.0	1.0, 30.0	<1, 31.0	1.0, 39.0	1.0, 57.0	<1, 57.0
Body Mass Index (BMI), kg/m^2								
Mean (SD)	32.7 (6.7)	34.0 (7.9)	32.3 (7.1)	31.3 (5.0)	31.2 (5.7)	31.5 (6.9)	31.9 (6.1)	32.1 (6.6)
Median	30.5	33.0	30.5	30.2	29.8	30.1	31.1	30.5
Min, Max								

SD = Standard deviation

TABLE 6. Patient Disposition
[Number (%) of Patients]

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg		
Randomized to Treatment	78	81	78	78	76	82	79	552
Withdrawn Prior to End of Treatment								
Lack of Efficacy	43 (55.1)	32 (39.5)	34 (43.6)	11 (14.1)	7 (9.2)	3 (3.7)	20 (25.3)	150 (27.2)
Adverse Event	6 (7.7)	7 (8.6)	6 (7.7)	5 (6.4)	8 (10.5)	5 (6.1)	6 (7.6)	43 (7.8)
Lack of Compliance	3 (3.8)	2 (2.5)	3 (3.8)	0 (0.0)	1 (1.3)	2 (2.4)	1 (1.3)	12 (2.2)
Pregnancy	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	4 (5.1)	3 (3.7)	1 (1.3)	6 (7.7)	6 (7.9)	2 (2.4)	6 (7.6)	28 (5.1)
Total	56 (71.8)	45 (55.6)	44 (56.4)	22 (28.2)	22 (28.9)	12 (14.6)	33 (41.8)	234 (42.4)
Completed Study[a]	22 (28.2)	36 (44.4)	34 (43.6)	56 (71.8)	54 (71.1)	70 (85.4)	46 (58.2)	318 (57.6)

[a] Based on investigator's response on termination case report form

TABLE 6. Patient Disposition
[Number (%) of Patients]

	Troglitazone Monotherapy			Combination Therapy: Troglitazone/Glyburide			Glyburide Monotherapy	Total
	200 mg	400 mg	600 mg	200 mg/12 mg	400 mg/12 mg	600 mg/12 mg		
Randomized to Treatment	78	81	78	78	76	82	79	552
Withdrawn Prior to End of Treatment								
Lack of Efficacy	43 (55.1)	32 (39.5)	34 (43.6)	11 (14.1)	7 (9.2)	3 (3.7)	20 (25.3)	150 (27.2)
Adverse Event	6 (7.7)	7 (8.6)	6 (7.7)	5 (6.4)	8 (10.5)	5 (6.1)	6 (7.6)	43 (7.8)
Lack of Compliance	3 (3.8)	2 (2.5)	3 (3.8)	0 (0.0)	1 (1.3)	2 (2.4)	1 (1.3)	12 (2.2)
Pregnancy	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Other	4 (5.1)	3 (3.7)	1 (1.3)	6 (7.7)	6 (7.9)	2 (2.4)	6 (7.6)	28 (5.1)
Total	56 (71.8)	45 (55.6)	44 (56.4)	22 (28.2)	22 (28.9)	12 (14.6)	33 (41.8)	234 (42.4)
Completed Study[a]	22 (28.2)	36 (44.4)	34 (43.6)	56 (71.8)	54 (71.1)	70 (85.4)	46 (58.2)	318 (57.6)

[a] Based on investigator's response on termination case report form

NDA 20-720/S-002 **Date of Review: July 28, 1997**

Sponsor: Parke Davis Pharmaceutical Research; Ann Arbor, MI

REVIEW OF TROGLITAZONE SUPPLEMENT 002

DRUG: Rezulin (Troglitazone).

Dosage formulation: Oral; Clinical formulation is amorphous form. Note: crystalline form is poorly bioavailable.

CATEGORY: Antidiabetic.

INDICATION: Combination with sulfonylureas for Type II Diabetes

PHARMACOLOGY COMMENTS ON SUBMISSION:

Troglitazone was originally approved for use in a limited population of type II diabetics for whom other treatments were ineffective. This supplement seeks to expand the treatment population to include a treatment with troglitazone in combination with sulfonylureas. No new pharmacology data were provided by the sponsor. Pharmacology believes that no new pharmacology data are necessary for this indication. Therefore, no review of pharmacology data is required.

Labeling and carcinogenicity issues that remained from the initial NDA have now been resolved:

1. Carcinogenicity: A final meeting with the executive CAC was held on July 22, 1997. The committee determined that the results in female rats noted at the high dose (presently in the label) could be removed from the label because the dose exceeded the MTD, the agent is non genotoxic, and the remaining doses were sufficiently high to provide a reasonable estimate of carcinogenic potential.
2. Labeling: Sponsor has provided labeling modifications basing comparison of human and animal exposures on AUC of parent + total or active metabolite. The request from the division was to provide data on parent + total metabolites. The sponsor provided data on parent + active metabolites. It was determined that since the general toxicity (e.g., heart, liver, etc.) was likely due to the mechanism of action of the troglitazone, these could be described on the basis of parent + active metabolite AUC, but that, according to the executive CAC, the carcinogenicity results should be based on parent + total metabolite AUC. The sponsor has complied with this request.

PHARMACOLOGY RECOMMENDATION:

Pharmacology recommends approval of NDA 20-720/S-002.

Ronald W. Steigerwalt 7/28/97

Ronald W. Steigerwalt, Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Johnston

NDA 20-720/S-003 **Date of Review: July 28, 1997**

Sponsor: Parke Davis Pharmaceutical Research; Ann Arbor, MI

REVIEW OF TROGLITAZONE SUPPLEMENT 003

DRUG: Rezulin (Troglitazone).

Dosage formulation: Oral; Clinical formulation is amorphous form. Note: crystalline form is poorly bioavailable.

CATEGORY: Antidiabetic.

INDICATION: Monotherapy for Type II Diabetics.

PHARMACOLOGY COMMENTS ON SUBMISSION:
Troglitazone was originally approved for use in a limited population of type II diabetics for whom other treatments were ineffective. In supplement 002, the patient population was expanded to include a treatment in combination with sulfonylureas. Supplement 003 seeks to expand use of Rezulin as monotherapy for type II diabetics. No new pharmacology data were provided by the sponsor. Pharmacology believes that no new pharmacology data are necessary for this indication. Therefore, no review of pharmacology data is required. All labeling and carcinogenicity issues that remained from the initial NDA have been resolved (see review of Supplement 002).

PHARMACOLOGY RECOMMENDATION:
Pharmacology recommends approval of NDA 20-720/S-003.

Ronald W. Steigerwalt 7/28/97

Ronald W. Steigerwalt, Ph.D.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Johnston

Johnston

MAY 22 1997

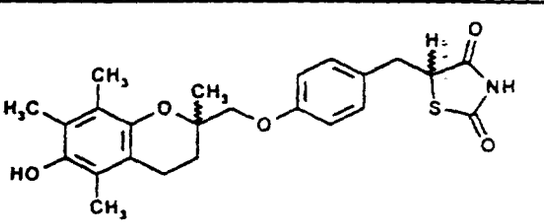
CHEMIST'S REVIEW

1. ORGANIZATION CDER/HFD-510 Division of Metabolism and Endocrine Drug Products	**2. NDA #** 20-720 **Approved:** 29-JAN-1997
3. NAME AND ADDRESS OF APPLICANT Parke-Davis Pharmaceutical Research Division Warner-Lambert Company 2800 Plymouth Road P.O. Box 1047 Ann Arbor, MI 48106-1047 (313) 966-5000	**4. SUPPLEMENT** S-002 Doc. 03-FEB-1997 Rec. 05-FEB-1997 **5. Name of the Drug** Rezulin **6. Nonproprietary Name** Troglitazone
7. SUPPLEMENT PROVIDES for a modification of the labeling. The labeling will be expanded to include Rezulin as monotherapy and combination therapy with sulfonyl ureas in patients with type II diabetes.	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY Hypoglycemic Agent, NIDDM.	**10. HOW DISPENSED** Rx	**11. RELATED** -N. A. -
12. DOSAGE FORM Tablet	**13. POTENCY** 200 and 400 mg	

14. CHEMICAL NAME AND STRUCTURE

Troglitazone
$C_{24}H_{27}NO_5S$
M.W. = 441.54
CAS Nº 97322-87-7



(1:1:1:1 stereoisomer mixture)
(±)-5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-ylmethoxy)benzyl]-2,4-thiazolidinedione

15. COMMENTS This supplement seeks approval to expand and modify the approved labeling to include Rezulin as monotherapy and combination therapy with sulfonyl ureas in patients with type II diabetes. Combination therapy of 600 mg Rezulin with 12 mg micronized glyburide provided a significant therapeutical improvement (combination therapy provided a mean decrease HbA1c of 2.65 % versus glyburide monotherapy after one year treatment) in the treatment of type II diabetes. There are no changes in manufacture. The patient population is the same than the for the approved drug, so considerations on the environmental impact have been already fulfilled in the original application.

16. CONCLUSIONS AND RECOMMENDATIONS From the chemistry viewpoint this supplement can be approved.

17. REVIEWER NAME (AND SIGNATURE) Xavier Ysern **DATE COMPLETED** 22-MAY-1997
Xavier Ysern, PhD

R/D INITIATED BY

filename: 20720s02.nda

DISTRIBUTION: Original: ⊠ NDA 20-482 cc: ⊠ HFD-510 Division File ⊠ CSO ⊠ Reviewer

Stephen K. Moore 5/22/97

NDA 20-720/S-002 & S-003
Rezulin™ 200 mg & 400 mg tablets

These NDA supplements contained no manufacturing changes.
Hence, No EERs were required.

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

July 29, 1997

NDA 20-720/S-002 and S-003
Ref. No. 65
Rezulin® (troglitazone) Tablets

Re: Draft Labeling/Phase IV Commitment

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our pending supplements S-002 and S-003 for Rezulin® (troglitazone) Tablets. Additional reference is made to my discussion with Mr. M. Johnston of your Division on July 28, 1997, regarding draft labeling.

Attached is the current prescribing information which includes the changes discussed with Mr. Johnston noted (Attachment 1). Additionally, a printed version which includes these changes is included (Attachment 2).

As discussed with the agency on several occasions, Parke-Davis commits to conduct

Should you have any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rp
t:\nda\20-720\072997-065

Attachment

Desk Copy: M. Johnston (2 copies)

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS

June 20, 1997

NDA 20-720/S-002 and S-003
Ref. No. 58
Rezulin™ (troglitazone) Tablets

Re: Draft Labeling

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our pending supplements S-002 and S-003 and to conversations with Dr. R. Misbin of your Division on June 12, 1997, regarding draft labeling. Reference is also made to our Special Supplement: Changes Being Effected submitted on June 17, 1997, to add a new 300 mg tablet. We have included reference to this new tablet in the How Supplied section of the draft labeling.

Attachment 1 is a revised package insert dated June 20, 1997, that is inclusive of all discussions and agreements with Dr. Misbin through June 12, 1997. Also included in the labeling is the revised toxicology information as requested by Dr. R. Steigerwalt in his telefax of March 10, 1997.

Attachment 2 contains the toxicology changes, the justification by Parke-Davis and the minutes of the FDA's February 27, 1997, PTCC meeting on troglitazone.

Should you have any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm t:\nda\20-720\062097-058

Attachments

Desk Copy: M. Johnston (2 copies)
R. Steigerwalt

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

June 11, 1997

NDA 20-720/S-002 and S-003
Ref. No. 55
Rezulin™ (troglitazone) Tablets

Re: Histopathological Slides

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our approved NDA 20-720 for Rezulin™ (troglitazone) Tablets and to the electronic mail message from Mr. M. Johnston of your Division on May 7, 1997, requesting histopathological slides from animals and humans.

The histopathological slides from the rat carcinogenicity study were sent to Dr. Akinwole Williams, Division of Cardio-Renal Drug Products, on May 14, 1997.

In Parke-Davis clinical studies a total of eleven deaths have been reported. After follow-up with each investigator, it has been determined that only 2 autopsies were performed. Since limited information can be obtained from only 2 patients and significant effort would be required to obtain the slides (including ethical considerations), we ask that this request be reconsidered.

Should you have any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm t:\nda\20-720\061197-55

Desk Copy: Dr. A. Williams, Division of Cardio-Renal Drug Products

Pharmaceutical
Research

PARKE-DAVIS

May 23, 1997

NDA 20-720/S-002, S-003
Ref. No. 52
Rezulin™ (troglitazone) Tablets

Re: 4-Month Safety Update

CENTER FOR DRUG
REC'D
MAY 27 1997
HFD-510
EVALUATION AND RESEARCH

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Please find (Volume 1) the 4-month Safety Update for supplements S-002 and S-003. Volumes 2 and 3 (Archival Copy only) contains Case Report Forms for patients who died or withdrew due to Adverse Events in Parke-Davis sponsored studies.

Should you have any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

REVIEWS COMPLETED

MEMO

CSO INITIALS DATE

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\022397-052

Attachments

Volume 1: Troglitazone (CI-991) Second Safety Update, RR 720-03863

Volume 2: Case Report Forms for Patients Who Died

Patient: 991-
991-
991-
991-

Volume 3: Case Report Forms for Patient Who Withdrew Due to Adverse Events

Patients: 991-
991-
991-
991-
991-
991-

Pharmaceutical
Research

SUPPL NEW CORR... ORIGINAL

RKE-DAVIS

May 16, 1997

NDA 20-720
Rezulin™ (troglitazone) Tablets

Re: Histologic Slides

Dr. Akinwole Williams
Food and Drug Administration
Center for Drug Evaluation and Researach
Office of Drug Evaluatin I
Division of Cardio-Renal Drug Products
Room 5002, WOC-II
1451 Rockville Pike
Rockville, Maryland 20852-1420

Dear Dr. Williams:

Reference is made to our approved NDA 20-720 for Rezulin™ (troglitazone) Tablets and to the request from Mr. M. Johnston of Metabolsim and Endocrine Drug Products on May 7, 1997, for certain histologic slides from our rat carcinogenicity study.

Enclosed please find the histologic slides.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\051697slides

cc: M. Johnston (HFD-510)

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

May 14, 1997

NDA 20-720
Ref. No. 50
Rezulin™ (troglitazone) Tablets —

Re: Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin™ (troglitazone) Tablets, to our pending supplements S-002 and S-003 and to a request from Dr. R. Misbin of your division on May 7, 1997.

Please find enclosed the additional analysis of fasting serum glucose for the This report was submitted on April 29, 1997. Patients have been divided into two groups, the first containing those treated by diet only prior to entering the study, the second containing those treated by oral anti-diabetic medication.

In addition, statistical analyses were performed separately for each group of patients (diet only and prior oral anti-diabetic medication). These analyses were performed as described in the end-of-study report.

For the ITT Population (Table 1 attached) patients treated with prior oral anti-diabetic medication in the three months prior to screening benefit from titrating the dose upwards through 200 mg qd, 400 mg qd, and 600 mg qd (decreases from baseline of -27, -23, and -47 mg/dl respectively). (Table 1)

For patients previously treated with diet alone there was no evidence of increased glycemic control with increased dose (decreases from baseline of -34 to -40 mg/dl for all three doses). (Table 2)

A Division of Warner-Lambert Company

If you have any additional questions, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\051497-50

Attachments

Desk Copy: Dr. R. Misbin

Pharmaceutical Research
2800 Plymouth Road Phone 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

May 5, 1997

NDA 20-720
Ref. No. 049
Rezulin™ (troglitazone) Tablets

Re: Response to Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin™ (troglitazone) Tablets.

Reference is also made to discussions with Dr. R. Misbin of your Division on April 28 and May 1, 1997.

As requested, please find attached the following information:

1. Requested reanalysis of study 991-057 adding 3 responders
2. Additional Summaries of Data on Troglitazone Monotherapy
3. Data from

This information was faxed to Dr. Misbin on May 1, 1997.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\050597-049

Attachments

Research

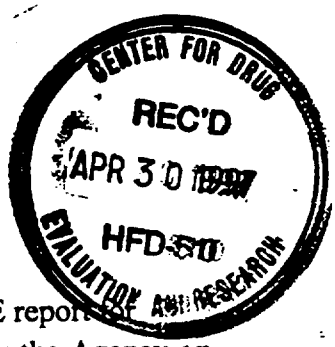
E-DAVIS

April 29, 1997

NDA 20-720
Rezulin™
(troglitazone) Tablets

Re: Periodic ADE Submission

Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857



Dear Sir or Madam:

Pursuant to 21 CFR 314.80, enclosed is the first quarterly periodic ADE report for Rezulin™ (troglitazone) Tablets, NDA 20-720, which was approved by the Agency on January 29, 1997.

This submission includes information on:

Initial Serious, Labeled Reports	0	Follow-Up Serious, Labeled Reports	0
Initial Non Serious Reports	18	Follow-Up Non Serious Reports	0
Initial 15-Day Alert Reports	2	Follow-Up 15-Day Alert Reports	0
Increased Frequency Reports	0		

As agreed upon during the March 25, 1997, telephone conversation between Rose Rogan, M.D., Vice President, Drug Safety Surveillance, Parke-Davis, and David Barash, RPH Chief, Division of Epidemiology and Surveillance, Food and Drug Administration, the time period covered by this report is January 30, 1997 to March 31, 1997.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

Mayra Ballina

Mayra Ballina, M.D.
Drug Safety Surveillance Physician
Worldwide Regulatory Affairs

bb
c:\nda\20-720\41097.dss

Attachments

ORIGINAL
P-001
DEU-510

Pharmaceutical Research
2800 Plymouth Road Phone 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

April 29, 1997

NDA 20-720
Ref. No. 048
Rezulin™ (troglitazone) Tablets

Re: Response to Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our approved NDA for Rezulin™ (troglitazone) Tablets. Reference is also made to our April 28, 1997 conversation with Dr. R. Misbin of your Division. Attached please find the following information:

Attachment 1: A double-blind, dose escalation study to investigate the efficacy and safety of oral GR921132X (200 mg, 400 mg and 600 mg) in the treatment of patients with Non-Insulin-Dependent Diabetes Mellitus.

Attachment 2: Patient Information Study 991-032.

Attachment 3: Abstract "Efficacy and Metabolic Effects of Troglitazone and Metformin in NIDDM."

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\ak t:\nda\20-720\042997.048

Attachments

Desk Copy: Dr. R. Misbin (HFD510)

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care

April 16, 1997

NDA 20-720 (Sec 2, Sec 3)
Ref. No. 46
Rezulin™ (troglitazone) Tablets

Re: Request for Information

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Per Dr. Misbin's request on April 11, 1997, please find attached our response on atrial natruretic peptide (ANP) values in Study 991-031.

If you have any additional questions, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, MPH
Director
Worldwide Regulatory Affairs

MT\rm
t:\nda\20-720\041697-46

Attachment

Desk Copy: Dr. Robert Misbin (HFD 510)

Pharmaceutical Research

RKE-DAVIS

NDA NO. [illegible] REF. NO. 37

NDA SUPPLEMENT NO. 3

ORIGINAL

February 14, 1997

NDA 20-720/S-003
Ref. No. 37
Rezulin™ (troglitazone) Tablets

Re: Supplement to an Approved
New Drug Application
User Fee I.D.

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Pursuant to 21 CFR 314.70, enclosed is a supplement to the approved New Drug Application 20-720 for Rezulin™ (troglitazone) Tablets. This supplement seeks approval to expand and modify the approved labeling to include Rezulin as monotherapy in patients with type II diabetes.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1997 application fee was transferred to the Food and Drug Administration in care of the Mellon Bank, Philadelphia, Pennsylvania on February 14, 1997.

All information to support this indication is contained in S-002, submitted February 3, 1996. Please cross reference all information in supplement S-002 for this application. The Generic Drug Enforcement Act Certification is attached.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

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Attachments

SNDA Copies: "Blue" Archive Vol. 1
"Tan" Medical Vol. 1

Company

Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

PARKE-DAVIS
People Who Care.

February 14, 1997

NDA 20-720
Ref. No. 36/S-002
Rezulin™ (troglitazone) Tablets

Re: User Fees

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our pending supplement for Rezulin™ (troglitazone) Tablets, submitted February 3, 1997.

It is our understanding from Ms. E. Galliers on February 14, 1997, that supplement S-002 for monotherapy and combination therapy with sulfonylureas is considered two new indications which require two separate user fees.

The application fee that was sent to Mellon Bank on January 23, 1997, should be applied to the pending supplement S-002 for combination therapy.

A separate supplement for the monotherapy indication will be submitted along with a separate user fee.

If you should have any questions or comments, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

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t:\nda\20-720\021497.036

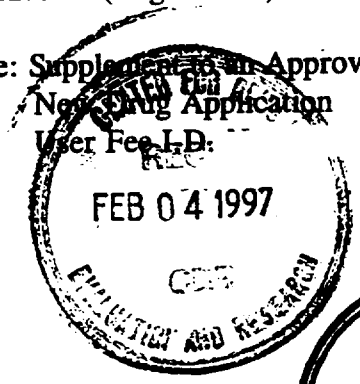
Pharmaceutical Research
2800 Plymouth Road Phone: 313-996-7000
Ann Arbor, MI
48105

ARKE-DAVIS
ple Who Care

February 3, 1997

NDA 20-720/S-002
Ref. No. 35
Rezulin™ (troglitazone) Tablets

Re: Supplement to an Approved
New Drug Application
User Fee I.D.:



Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products (HFD-510)
Document Control Room 14B-19
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Pursuant to 21 CFR 314.70, enclosed is a supplement to the approved New Drug Application 20-720 for Rezulin™ (troglitazone) Tablets. This supplement seeks approval to expand and modify the approved labeling to include Rezulin as monotherapy and combination therapy with sulfonylureas in patients with type II diabetes.

The use of Rezulin and sulfonylurea combination therapy provides a significant therapeutic advance in the treatment of the type II diabetes. Combination therapy of 600 mg Rezulin with 12 mg micronized glyburide provided a mean decrease in HbAlc of 2.65% versus glyburide monotherapy after one year of treatment. Additionally, the dosing of Rezulin monotherapy differs from that when Rezulin is used according to the instructions in the currently-approved labeling for insulin combination therapy. Rezulin is, therefore, likely to be used incorrectly if used off-label. For these two reasons we feel a priority review should be considered for this important efficacy supplement.

As required under the Prescription Drug User Fee Act of 1992, 50% of the 1997 application fee has been sent to the Food and Drug Administration in care of the Mellon Bank, Philadelphia, Pennsylvania on January 23, 1997.

Marketing exclusivity information and the Generic Drug Enforcement Act Certification are in Item 13, contained in Volume 1 of this SNDA. Also included is a complete copy of the Confidential Environmental Assessment (EA) and the Freedom of Information (FOI) EA. These documents are identical to what was submitted to the NDA on November 1, 1996, Ref. No.'s 16 and 17. The EA was originally written to include all patients with type II diabetes.

Please refer to the attached Form FDA 356h and the SNDA Index which detail the complete contents of this supplemental NDA. The Integrated Summary of Safety was submitted to the NDA December 19, 1996 (Ref. No. 26).

SAS data sets from the efficacy studies are included in both the archival and Biometrics review copy of SNDA Item 10 of this submission. The diskettes have been scanned for all known computer viruses using Norton Anti-Virus for Windows NT.

If there are any questions or comments regarding this submission, please contact me at 313/996-5000 or FAX 313/998-3283.

Sincerely,

Mary E. Taylor, M.P.H.
Director
Worldwide Regulatory Affairs

MT\rm
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Attachments

SNDA Copies:

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"Green" Biometrics	Vol. 1, 27 - 45